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MEDICAL DEVICE QUALITY SYSTEMS MANUAL: A SMALL ENTITY COMPLIANCE GUIDE

First Edition

(Supersedes the Medical Device Good Manufacturing Practices Manual)

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CENTER FOR
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FOREWORD

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA), develops and implements national programs to protect the public health in the fields of medical devices and radiological health. These programs are intended to assure the safety, effectiveness, and proper labeling of medical devices, to control unnecessary human exposure to potentially hazardous ionizing and non-ionizing radiation, and to assure the safe, efficacious use of such radiation.

The Center publishes the results of its work in scientific journals and in its own technical reports. These reports disseminate results of CDRH and contractor projects. They are sold by the Government Printing Office and/or the National Technical Information Service. Many are available via the FDA home page on the World Wide Web at: http:\\www.fda.gov.

We welcome your comments and requests for further information.

D. Bruce Burlington, M.D.
Director
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PREFACE

The Medical Device Amendments of 1976 mandated the establishment of "an identifiable office to provide technical and other nonfinancial assistance to small manufacturers of medical devices to assist them in complying with the requirements of the Federal Food, Drug, and Cosmetic Act." The Division of Small Manufacturers Assistance (DSMA) in the Office of Health and Industry Programs (OHIP) was established to meet this requirement. DSMA develops educational materials and sponsors workshops and conferences to provide firms with a firsthand working knowledge of medical device requirements and compliance policies.

This manual covers the Quality System regulation and the basic Good Manufacturing Practices (GMP) requirements that all manufacturers and distributors must consider when they plan to manufacture medical devices, including medical device kits, trays or packs, for distribution in the United States. Model procedures and sample forms are also included in the manual to assist manufacturers.

Adherence to the medical device Quality System regulation makes good business sense and also serves public health aims -- two very good reasons for the Food and Drug Administration (FDA) to encourage compliance. However, a prerequisite to complying with a regulation is a clear understanding of its content. Recognizing this fact, the Division of Small Manufacturers Assistance (DSMA) developed this manual to help manufacturers increase their knowledge of medical device GMP requirements and FDA compliance policies. DSMA also uses this manual at quality system workshops conducted throughout the country.

The Quality System regulation outlines the minimum elements of a system for designing and producing a medical device. Manufacturers of medical devices commonly find that their quality needs are broader than these basic elements because of the additional need to meet company quality claims as required by paragraph 501(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act and to meet customer needs and requirements.

The DSMA staff and the Office of Compliance (OC) in the Center for Devices and Radiological Health (CDRH) provided valuable assistance in preparing this manual.

For further information, contact the appropriate office within CDRH or call DSMA at 800-638-2041, 301-443-6597 or FAX 301-443-8818. Comments on this manual, related workshops, and other DSMA activities are always welcome.

Lireka P. Joseph, Dr.P.H.
Director

Office of Health and Industry Programs

NOTE TO MANUFACTURERS OF MEDICAL DEVICES

The Quality System (QS) regulation indicates the required end result rather than specifically prescribing how a manufacturer is to comply with this regulation. It is the responsibility of the manufacturer to use good judgment when developing a quality system which appropriately applies the QS regulation to their specific products and operations. The manufacturer, not FDA, bears overall responsibility for the production of high-quality products.

Nevertheless, FDA recognizes that manufacturers may benefit from having guidance, model procedures, and sample forms that others have developed or adopted in an effort to comply with the intent of the regulation. The guidance in this manual includes discussion on the entire QS regulation, plus it provides multiple examples of procedures and forms which can be adopted and modified by manufacturers as appropriate.

We have included a variety of model procedures and sample forms in this manual. However, these are not meant to be official statements of FDA policy. Rather, they represent a compilation of examples that firms may find useful in understanding how some manufacturers have successfully complied with QS and/or GMP requirements. Before any model procedure or form is adopted into a quality system program, the applicability and suitability to a particular device and manufacturing operation should be carefully examined. This manual will assist you in developing a quality system that meets the intent of the FDA Quality System regulation.

FDA also recognizes the continuing need to use innovative approaches, particularly in dealing with small businesses that could be unnecessarily adversely affected by federal regulations. It is hoped that the information in this manual will assist manufacturers in their efforts to establish and maintain a quality system that enhances business. The Office of Compliance at 301- 594-4692 or DSMA at 800-638-2041, FAX 301-443-8818, can be contacted for additional assistance and information.

This manual can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington D.C. 20402, telephone 202-512-1800, and from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161, telephone 703-487-4650. This manual is also available to all manufacturers through the World Wide Web at: http:\\www.fda.gov.

Sincerely yours,

John F. Stigi
Director
Division of Small Manufacturers Assistance

ABSTRACT

A. Lowery, J. Strojny, and J. Puleo, Project Officers. Division of Small Manufacturers Assistance, Office of Health and Industry Programs. Medical Device Quality Systems Manual: A Small Entity Compliance Guide. HHS Publication FDA 97-4179 (December 1996).

This manual covers requirements of the Quality System regulation that manufacturers of medical devices must consider when they design devices, or when they manufacture, contract manufacture, remanufacture, process, repack, or relabel finished medical devices intended to be commercially distributed. The manual contains articles that explain the various good manufacturing practices (GMP) requirements such as design controls, process validation, calibration, device master records, component control, etc., along with related topics such as labeling. It also contains examples of forms, procedures, decals, etc. Manufacturers may use this guidance when developing their quality system.

This manual incorporates changes required by the Safe Medical Devices Act of 1990 and the Medical Device Amendments of 1992. This manual is an update of HHS publication FDA 91-4179, "Medical Device Good Manufacturing Practices Manual, Fifth Edition."

This manual is used in the Division of Small Manufacturers Assistance (DSMA) medical device workshops.

CONTENTS

1 THE QUALITY SYSTEM REGULATION

INTRODUCTION

The current Good Manufacturing Practices (GMP) requirements set forth in the Quality System (QS) regulation are promulgated under section 520 of the Food, Drug and Cosmetic (FD&C) Act. They require that domestic or foreign manufacturers have a quality system for the design and production of medical devices intended for commercial distribution in the United States. The regulation requires that various specifications and controls be established for devices; that devices be designed under a quality system to meet these specifications; that devices be manufactured under a quality system; that finished devices meet these specifications; that devices be correctly installed, checked and serviced; that quality data be analyzed to identify and correct quality problems; and that complaints be processed. Thus, the QS regulation helps assure that medical devices are safe and effective for their intended use. The Food and Drug Administration (FDA) monitors device problem data and inspects the operations and records of device developers and manufacturers to determine compliance with the GMP requirements in the QS regulation.

The QS regulation is in Part 820 of Title 21 of the *Code of Federal Regulations* (CFR). This regulation covers quality management and organization, device design, buildings, equipment, purchase and handling of components, production and process controls, packaging and labeling control, device evaluation, distribution, installation, complaint handling, servicing, and records. The preamble describes the public comments received during the development of the QS regulation and describes the FDA Commissioner's resolution of the comments. Thus, the preamble contains valuable insight into the meaning and intent of the QS regulation.

The QS regulation is reprinted in the appendix of this manual.

FLEXIBILITY OF THE GMP

Manufacturers should use good judgment when developing their quality system and apply those sections of the QS regulation that are applicable to their specific products and operations. Section 820.5 of the QS regulation requires that, "Each manufacturer shall establish and maintain a quality system that is appropriate for the specific device(s) designed or manufactured, and that meets the requirements of this part." The word "appropriate" means that the rule is a flexible regulation. However, if manufacturers decide to not implement certain GMP requirements which are qualified by the term "where appropriate," they should document their justification for nonimplementation. The justification should show that not implementing a requirement is not reasonably expected to result in product that does not meet specifications or failure to carry out any necessary corrective action [820.1(a)(30]. Operating within this flexibility, it is the responsibility of each manufacturer to establish requirements for each type or family of devices that will result in devices that are safe and effective, and to establish methods and procedures to design, produce, and distribute devices that meet the quality system requirements. FDA has identified in the QS regulation the essential elements that a quality system shall embody for design, production and distribution, without prescribing specific ways to establish these elements. Because the QS regulation covers a broad spectrum of devices and production processes, it allows some leeway in the details of quality system elements. It is left to manufacturers to determine the necessity for, or extent of some quality elements and to develop and implement specific procedures tailored to their particular processes and devices. For example, if it is impossible to mix up labels at a manufacturer because there is only one label or one product, then there is no necessity for the manufacturer to comply with all of the GMP requirements under device labeling.

The medical device QS regulation requires an "umbrella" quality system intended to cover the design, production, and distribution of all medical devices from simple surgical hand tools to very complex computerized axial tomography (CAT) scanners. It is not practical for a regulation to specify details of quality system elements for such a wide range of products. Rather, the QS regulation specifies general objectives such as use of trained employees, design reviews, design validation, calibrated equipment, process controls, etc., rather than methods, because a specific method would not be appropriate to all operations.

In most cases, it is left to the manufacturer to determine the best methods to attain quality objectives. In some cases, however, the QS regulation does specify the particular type of method to be used, such as written procedures or written instructions. This does not mean, however, that manufacturers cannot vary from the method specified if the intent of the GMP requirement can be met by another method such as using an engineering drawing plus a model device as manufacturing instructions. Written procedures are not restricted to paper copies. Written procedures may be filed and distributed by automated data processing equipment. This flexibility is allowed by section 820.180.

Typically, large manufacturers will have a quality system that exceeds the medical device QS regulation. Small manufacturers will typically have a proportionally simpler system. FDA recognizes: that a small manufacturer may not need the same amount of documentation that a large manufacturer does in order to achieve a state-of-control; and, that some of records maintained to fulfill the GMP requirements for written procedures may not be as long and complex for a small manufacturer.

After a manufacturer establishes a quality system, it should be maintained. Each manufacturer should assure that with growth and process or product changes their quality system is still adequate. This assurance is obtained through change control, day-to-day observance of operations, and by periodic audits of the quality system. The auditor should first identify the elements of the company's quality system. Next the audit should determine how well each element is functioning, and then determine its adequacy with respect to the intent of the device GMP requirements and meeting the company's quality claims.

MANUAL CONTENTS

To aid auditors, QA managers, and others, this manual provides guidance in the interpretation of the GMP requirements, and demonstrates the flexibility of the QS regulation in its application to diverse devices, manufacturing processes, and manufacturers. In the absence of guidance from FDA, manufacturers may rely on industry, national, and international consensus standards or guidances to meet GMP requirements.

This manual was also developed to aid manufacturers in completing, maintaining, or expanding their quality system. Contents include educational materials, aids, and examples of how to implement elements of a quality system, together with detailed examples of procedures, control forms, and associated data. The examples of typical procedures, drawings, and forms found in this manual were derived from quality systems in the device industry. These materials are not meant to describe universally applicable elements of a quality system that can be used unchanged by any manufacturer. Of course, a form or aid as presented in this manual may be suitable for direct use for a specific device and operation; however, in general, manufacturers will need to use care in adopting and modifying a selected form or procedure to meet the specific quality system needs of their devices and operations.

This manual is arranged as if the reader were starting a new business. That is, as if an entrepreneur were sequentially:

1. **obtaining information on GMP requirements;**
2. **determining the appropriate quality system needed to control the design, production and distribution of the proposed device;**
3. **designing products and processes;**
4. **training employees;**
5. **acquiring adequate facilities;**
6. **purchasing and installing processing equipment;**
7. **drafting the device master record;**
8. **noting how to change the device master records;**
9. **procuring components and materials;**
10. **producing devices;**
11. **labeling devices;**
12. **evaluating finished devices;**
13. **packaging devices;**
14. **distributing devices;**
15. **processing complaints and analyzing service and repair data;**
16. **servicing devices;**
17. **auditing and correcting deficiencies in the quality system; and**

18. preparing for an FDA inspection.

If manufacturers perform these activities as required by the QS regulation and as expounded in this manual, they should be prepared for a GMP inspection of their operations by an FDA investigator.

Manufacturers and importers of medical devices shall also comply with the Medical Device Reporting (MDR) regulation, 21 CFR Part 803, which requires that serious complaints be reported to FDA. MDR is related to the GMP complaint and failure investigation requirements, which are covered in Chapter 15. If manufacturers comply with the QS regulation and guidance in this manual and in other sources, there is a high probability that they will reduce the frequency of reportable events.

GMP APPLICATIONS AND EXEMPTIONS

The QS regulation applies to finished devices intended to be commercially distributed for human use unless there is an approved exemption in effect. GMP exemptions are codified in the classification regulations 21 CFR 862 to 892. The exemption of most Class I devices from design controls is in section 820.30(a).

Certain components such as blood tubing and major diagnostic x-ray components are considered by FDA to be finished devices because they are accessories to finished devices. The manufacturer of such accessories is subject to the QS regulation when the accessory device is labeled and sold separately from the primary device for a health-related purpose to a hospital, physician, or other user.

The designation of a device as a "custom" or “customized” device does not confer a GMP exemption.

Contract manufacturers and specification developers shall comply with the sections of the QS regulation that apply to the functions they perform.

Contract test laboratories are considered an extension of a manufacturer's quality system and presently are not routinely scheduled for GMP inspections. The finished device manufacturer shall meet the requirement of the QS regulation, particularly 820.50, Purchasing, when they obtain products or services. Internal test laboratories, however, that are part of a corporate manufacturer that provides services to individual corporation factories should meet GMP requirements. Internal laboratories are inspected as part of the FDA GMP inspection of the member factories.

Situations are discussed in the remainder of this chapter where various manufacturers are exempt from the QS regulation or are not routinely inspected. However, these manufacturers are still subject to the FD&C Act. If these manufacturers or any manufacturer render devices unsafe or ineffective, the devices are adulterated and/or misbranded and the manufacturers are subject to the penalties of the FD&C Act.

Exemptions

FDA has determined that certain types of establishments are exempt from GMP requirements; and
FDA has defined GMP responsibilities for others. Exemption from the GMP requirements does not exempt manufacturers of finished devices from keeping complaint files (820.198) or from general requirements concerning records (820.180). Sterile devices are never exempted from GMP requirements. A device that normally would be subject to GMP requirements may be exempt under the following conditions:

- **When FDA has issued an exemption order in response to a citizen's petition for exemption,**
- **When FDA, in the absence of a petition, has exempted the device and published the exemption in the Federal Register,**
- **When the device is exempted by FDA classification regulations published in the Federal Register and codified in 21 CFR 862 to 892,**
- **When the device is an investigational intraocular lens (IOL) and meets the requirements of the investigational device exemption (IDE) regulation for IOL's, and**
- **Through a policy statement, FDA may decide not to apply GMP requirements to some types of devices and processes although the devices may not have been exempted from GMP requirements.**

Manufacturers should be aware of the GMP exemption status of their devices. In addition, manufacturers should keep on file records of any specific GMP exemption granted to them by FDA. Upon request during a factory visit, the exemption records need to be shown during normal business hours to the FDA investigator in order to verify that an exemption has been granted.

Component Manufacturers

A "component" is defined by 820.3(c) as "any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device." Component manufacturers are excluded from the QS regulation by 820.1(a)(i). Current FDA policy is to rely upon the finished device manufacturer to assure that components are acceptable for use. Component manufacturers are not routinely scheduled for GMP inspections; however, FDA encourages them to use the QS regulation as guidance for their quality system.

When finished device manufacturers produce components specifically for use in medical devices they produce, whether in the same building or another location, such production of components is considered part of the device manufacturing operations, and the production should comply with the QS regulation.

Accessory devices [807.20(a)(5)] such as hemodialysis tubing or major diagnostic x-ray components, that are packaged, labeled, and distributed separately to a hospital, physician, etc., for health-related purposes are sometimes inappropriately referred to as components. However, FDA considers them finished devices because they are suitable for use or capable of functioning and are distributed for health-related purposes; and the QS regulation applies to their manufacture. Similarly, a device or component including software that is sold as an addition to a finished medical device to augment or supplement its performance is also termed an accessory. An accessory to a medical device is considered a finished device and, therefore, is subject to the QS regulation.

Remanufacturers

A remanufacturer is any person who processes, conditions, renovates, repackages restores or does any other act to a finished device which has been previously distributed to significantly change the finished device's performance or safety specifications or intended use from that established by the original finished device manufacturer. Remanufacturers are considered manufacturers. As such, these manufacturers are subject to inspection by FDA and shall meet the applicable requirements of the medical device QS regulation. These manufacturers shall establish and implement quality systems to assure the safety and effectiveness of the devices that are distributed. Such activities include drafting of master records, rebuilding per the master records, inspection and testing, calibration of measurement equipment, control of components, updating of labeling, processing of complaints, and any other GMP requirement applicable to the activities being performed.

Remanufacturers are also required to comply with the labeling requirements of 21 CFR 801.1(c). This labeling regulation requires that where the person or manufacturer named on the label of the device is not the original manufacturer, the name shall be qualified by an appropriate phrase which reveals the connection that person has with the device, e.g., remanufactured by XYZ Company.

Custom Device Manufacturers

Section 520(b) of the FD&C Act and the IDE regulation (21 CFR Part 812) define a custom device. Custom devices are exempt from certain statutory requirements. For example, manufacturers of custom devices are not required to comply with premarket approval requirements (Section 515) and are exempt from premarket notification requirements [Section 510(k)]. Custom devices are NOT exempt from the GMP requirements. Current FDA policy, however, is to not inspect manufacturers of custom devices. Manufacturers of custom devices should comply with the GMP requirements while considering the flexibility allowed.

Contract Manufacturers

A person(s) that manufactures a finished device under the terms of a contract with another manufacturer is a contract manufacturer. The agreement between the manufacturers should be documented in a written contract. Contract manufacturers of finished devices shall comply with applicable requirements of the quality system and shall register their establishment with FDA. Depending on the circumstances, both the contractor and manufacturer may be held jointly responsible by FDA for the activities performed.

Contract Testing Laboratories

Contract laboratories that designs or test components or finished devices for a manufacturer are considered an extension of the manufacturer's quality system. These laboratories may provide services to a number of customers, many of which are not medical device manufacturers. These contract laboratories are not subject to routine GMP inspections. Through the conduct of quality audits or other means, the finished device manufacturer is responsible for assuring that equipment and procedures used by a lab are adequate and appropriate (820.50). However, an internal test laboratory, if part of a manufacturer that does testing for various facilities within the corporation, is subject to inspection when FDA GMP inspections are conducted at the individual manufacturing facilities. That is, the test laboratory is simply a part of a medical device manufacturer of which all device-related divisions shall comply with the QS regulation.

Repackagers, Relabelers, and Specification Developers

Repackaging and relabeling of a device and specification development are defined as manufacturing in 21 CFR Part 807, Establishment Registration and Device Listing for Manufacturers of Devices. Some definitions from 807.3(d) are reprinted below because they affect the applications of the QS regulation.

(d) "Manufacture, preparation, propagating, compounding, assembly, or processing" of a device means the making by chemical, physical, biological, or other procedures of any article that meets the definition of a device in section 201(h) of the Act.

These terms include the following activities:

(1) Repackaging or otherwise changing the container, wrapper, or labeling of any device package in furtherance of the distribution of the device from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer;

(2) Initial distribution of imported devices; or

(3) Initiation of specifications for devices that are manufactured by a second party for subsequent commercial distribution by the person initiating specifications.

As defined above, repackaging and relabeling are manufacturing operations. Further, a repacker, repackager or relabeler is a manufacturer per 820.3(o) and subject to the applicable requirements of the QS regulation. Individuals are repackers or relabelers if they:

- **package and/or label previously manufactured finished devices or accessories;**
- **receive finished devices in bulk (e.g., surgical tubing, syringes, media, etc.,) and repacks them into individual packages and label them;**
- **receive previously manufactured devices that have been packaged and labeled by another manufacturer, and combine them into a kit with other unpackaged devices which are received in bulk.**

Individuals are not considered repackers or relabelers or a manufacturer for purposes of applying the QS regulation if they pack only previously packaged and labeled individual devices into

packages for the convenience of the user. (Note that this activity is essentially the same as a drug store employee placing packaged items into a bag labeled with the name of the drug store.)

A distributor who only adds a label bearing their name and address is exempt from the GMP requirements. A manufacturer simply affixing a sticker label bearing the distributor's name and address would not require record keeping demonstrating compliance with labeling controls requirements.

Specification developers provide specifications to contract manufacturers, who produce devices to meet the specifications. The contract manufacturer may package and label the device, or the finished device may be shipped to the specification developer for packaging and labeling.

Specification developers are manufacturers and are subject to the GMP requirements that apply to the activities they conduct, such as various design controls including correct transfer of the design information to a contract manufacturer [820.30(h)]. This activity, in turn, requires an adequate device master record (820.181) and adequate change control [820.40(b)]. Further, if the product carries the specification developer's label, the developer is responsible for maintaining a complaint file and processing complaints, plus maintaining the device specifications and other appropriate documents in the device master record.

Initial Distributors of Imported Devices

The initial distributor is the foreign manufacturer's official correspondent with the FDA. With regards to the GMP, this initial distributor is responsible for maintaining complaint files and general record keeping requirements. A procedure shall be established and maintained for receiving, reviewing, and evaluating complaints. All complaints, including oral complaints, are to be processed in a uniform and timely manner. These complaints shall be evaluated to determine whether or not they require reporting to FDA under 21 CFR part 804 or 803, Medical Device Reporting. The initial distributor is also required to evaluate all complaints to determine whether an investigation is necessary, as well as complying with all other requirements in 820.198, Complaint Files. See Chapter 15 in this manual for more complete guidance on handling complaints.

2 QUALITY SYSTEMS

INTRODUCTION

The Quality System (QS) regulation requires that each manufacturer shall establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured (820.5 and 820.20). The GMP requirements are harmonized with the International Organization for Standards (ISO) 9001:1994 and ISO DIS 13485. The quality system should be an integrated effort -- a total systems approach, to satisfy the particular safety and performance needs of a specific manufacturer, product, and user-market. The quality assurance (QA) activities do not simply consist of inspection and testing spot solutions or "fire-fighting," no matter what the product is or how small the manufacturer. In all cases, quality should be considered at the earliest stages in every significant area that has an effect on the quality, safety, and effectiveness of the device. These areas include product development, design verification and validation, component and/or supplier selection, documentation, development of labeling, design transfer, process development and validation, pilot production, routine manufacturing, test/inspection, device history record evaluation, distribution, service or repair, and complaints. Complaints and, of course, favorable comments constitute customer feedback that may result in improvements in the device, labeling, packaging or quality system.

Most important of all is management commitment. Management and employees should have the correct attitude if their quality system program is to be effective. Quality consciousness should be developed in every employee. Each person should be made aware of the importance of his or her individual contributions in the overall effort to achieve an acceptable level of quality.

After a quality system is in place and checked, it should not be allowed to stagnate -- it should continue to be dynamic. The system remains dynamic through continuous feedback, "big-picture" monitoring by system audits, management review, and corrective and preventive action. Sufficient

personnel with necessary education, background, and experience should be in all departments to ensure that quality system activities are properly and adequately performed.

The result is an organization that is operating in a known state-of-control for the device design, process design, manufacturing processes, and records. A properly functioning quality system results in increased safety and effectiveness of the device, reduced liability exposure, reduced regulatory exposure, increased customer satisfaction, less scrap, lower costs, much less confusion, higher employee morale, and, as a result, higher profits.

There are several QA systems in common use, including quality control, good manufacturing practices, product design assurance, the ISO 9000 series of international QA standards, and total quality assurance. Quality control is a minimal system which emphasizes test and inspection. The QS regulation is a government mandated QA system for medical device manufacturers. It emphasizes device, labeling, packaging and process design and all aspects of production: facilities, equipment, design development, design and production documentation, correct design transfer, production control, production records and feedback. Total quality assurance is a system which emphasizes that: all employees and suppliers are responsible for their activities; design requirements are established and met; process requirements are established and met; all production activities are controlled; finished product specifications are met; and feedback results in appropriate corrections.

Product design assurance is a QA system which assures that customer needs are determined, and that product design requirements are established and met. The ISO 9000 series of QA standards ranges from basic quality control to very significant design and production systems.

ISO 9001 is the most comprehensive because it covers design, production, servicing and corrective/preventive activities. The FDA GMP requirements are slightly more extensive because they include extensive coverage of labeling, and complaint handling.

An ideal system for quality assurance is discussed in order to explain the concept of a system. An ideal QA system is composed of an organization that executes a QA program according to documented policy and specifications in order to achieve stated objectives as shown in Figure 2.1.

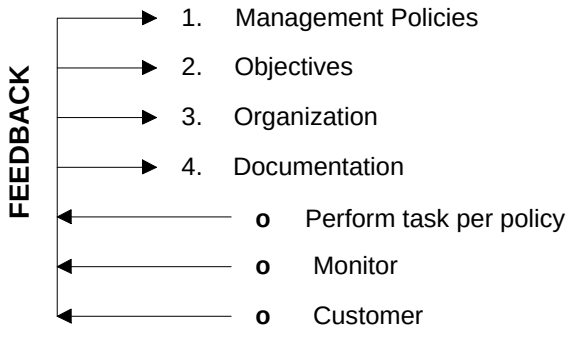

Figure 2.1 Elements of a Quality System

The written policies and objectives are set by management and are influenced by outside factors such as customer requirements, standards, and regulations. For example, the customer requirements and needs and resulting device specifications should be known to be correct, as these are based on market

research, technical and medical considerations, consensus standards, review of existing devices, environmental and compatibility considerations, and design review. The objectives are to produce safe and effective devices at a profit. Ideally, the quality system includes everyone in the company as everyone is fully committed to the quality system program. In addition, however, quality assurance departments such as design QA and production QA are established to help achieve specific objectives. Tasks to be performed to meet these objectives are described in procedures and other documents.

Documentation for a quality system is composed of: product-specific technical documentation such as engineering drawings, component purchase specifications, procedures for manufacturing processes and testing; labels, etc.; and general quality system documentation, such as standard operating procedures (SOP's) for employee training, audits, etc., that are applicable for all products. All activities and product quality are monitored; and any deviations from device and process specifications and company policies are fed back into the system where the deviations are corrected. Likewise, complaint and service information are processed and fed back for appropriate corrections. If the required activities including the feedback are performed, the quality system is self correcting and, thus, the manufacturer is operating in a state-of-control. FDA requires manufacturers of medical devices to operate in a state-of-control.

QUALITY SYSTEM PRACTICES

An adequate and properly implemented quality system such as the one required by the QS regulation or ISO 9001, because of its broad scope, has a high likelihood of preventing the design, manufacture, and shipment of defective products. Basic quality controls such as inspection and testing, are important parts of a quality system because they provide information that should be fed back into the program where action can be taken to correct root causes of quality problems. Identifying and solving quality problems is a core requirement of the QS regulation. This approach is in contrast to merely applying superficial corrections by pass/fail quality-control inspection including rework of finished product or in-process assemblies.

Feedback is necessary to verify the adequacy of the design, manufacturing processes, and the controls used. It also helps trigger corrective action to solve root causes of quality problems rather than just performing rework.

Design Controls

Each manufacturer is required by regulation to establish and maintain design control procedures for any class III or class II device, and a selected group of class I devices. The class I devices subject to design controls are devices automated with computer software and the following specific devices:

SECTION	DEVICE
868.6810	Catheter, Tracheobronchial Suction
878.4460	Glove, Surgeon’s
880.6760	Restraint, Protective
892.5650	System, Applicator, Radionuclide, Manual
892.5740	Source, Radionuclide Teletherapy

Because the intrinsic quality level of devices and processes is established during the design phase, the quality system program should include this phase if the program is to assure overall quality,

meet customer requirements, meet company quality claims, and comply with the intent of the FD&C Act. The terms "product assurance" and "design QA" are often used to identify the quality system activities related to product design. The QS regulation uses the term "design controls." A product assurance system or design QA system combined with a production QA system constitutes a total quality system.

Quality system, production, regulatory, and other appropriate personnel should participate in the review, evaluation, and documentation of the components, device, and process design. It is from data established during this preproduction phase that all other activities derive such as, purchasing, processing, and testing. Development and validation data are also useful in cases of regulatory or product liability actions to show that the design and manufacturing processes were well conceived and properly validated, reviewed, and documented.

Total quality systems extend from customer requirements through development and production to customer use and feedback. Thus total quality systems encompass the medical device law and regulations, particularly the QS regulation. The FD&C Act, and its implementing regulations such as those for Labeling, Premarket Notification, Investigational Device Exemptions (IDE), Premarket Approval (PMA), and GMP requirements impact the quality of devices at various times during the design product life-cycle. The IDE, PMA, 510(k), labeling and QS regulation with their preproduction and production requirements constitute a total quality system. For example, Section 501(c) of the Act states that a product is adulterated if it does not have a quality equal to the quality stated or implied by the product labeling. Analysis of device recall problem data by FDA has shown that such problems are divided almost equally between design and production. Thus, a production quality assurance program is not sufficient to produce safe and effective devices -- design shall also be covered. A design quality assurance system is required by the QS regulation.

Two other reasons for having a total quality system are 21 CFR Part 803, Medical Device Reporting (MDR), and product liability. MDR requires manufacturers of medical devices to report to FDA certain adverse events that they receive from any source. Product liability actions are often the result of poor design, labeling, and manufacturing. Reporting and liability exposure are reduced by using a total quality system.

Intrinsic or desired quality is established by the design specifications for the product, its components, and the manufacturing processes. Complying with the QS regulation assures that the manufacturing processes can consistently achieve desired levels of quality and that the finished device meets its device master record specifications. This result is a significant quality step. However, if the device as designed is of poor quality, the GMP production controls will only assure that a poor quality device is manufactured. Thus, the QS regulation requires an overall quality system program, which embraces evaluation of customer needs; product design; verification and validation; labeling development and control; all manufacturing and control activities; and customer feedback.

Component Selection

Component and raw material specifications developed during the design phase should be well conceived and adequate for their intended purpose. New components or components for an unusual application need to be verified (qualified) for the intended use. In some cases, where large quantities of components or raw materials are involved, the specifications should include valid and well

understood methods of sampling and acceptance. These specification and sampling/acceptance plans should also be accessible and acceptable to suppliers. The specifications are device master record (DMR) spec document or the specifications appear in a DMR drawing or procedure.

Manufacturers shall establish and maintain procedures to ensure their purchased and otherwise received products and services conform to their specified requirements. The manufacturers shall then assess their suppliers, contractors, and consultants based on their ability to meet the established specifications. When possible, an agreement shall be established to include that the suppliers, contractors, and consultants will notify the manufacturer of any changes in the product or service that may affect the quality of a finished device.

Labeling Content

The regulations in 21 CFR Part 801, Labeling; Part 809, In Vitro Diagnostic Products for Human Use; and Part 812, Investigational Device Exemptions, are intended to control the content of labeling. Likewise, 21 CFR Part 807, Premarket Notification; and Part 814, Premarket Approval and 820.30, Design Controls, help control the content of labeling by design and premarket submissions. The intent of these regulations and the FD&C Act is for manufacturers to have a labeling control program such that their labeling always complies with the regulations and meets the needs of the users. By a formal process under a total quality system during the design phase, clear and concise printed and/or software labeling are written and reviewed; and the ink substrate and attachment methods for printed labeling are developed. Such labeling is designed to meet customer and regulatory requirements. Thereafter, the procurement, use of the correct label, and the correct attachment of labels is assured under a manufacturer's quality system elements for these activities.

Process Quality

Manufacturing methods and processes to be used should be developed, equipment selected, and processes and methods qualified. For all significant processes such as welding, molding, lyophilizing, sterilizing, and packaging/sealing where the output cannot be fully verified, the qualification should include a full validation of the processes. The output may not be fully verified for economic, technical, or practical reasons and thus validation is needed. Production specifications and methods employed in manufacturing should result in standard in-process and finished products without excessive sorting or reprocessing. Inspection and test methods should be developed that will adequately monitor product characteristics to make certain these are within the acceptable specifications. These methods should be developed, evaluated, validated where necessary, and documented during the product and process development phase. The methods should be implemented at the beginning of routine production.

Any adverse effects the manufacturing processes, manufacturing materials, or equipment may have on device safety and performance should be identified. Where necessary, procedures have to be developed, implemented, and monitored to control these characteristics. Quality system personnel should participate in the timely (i.e., early) development of special controls, test or inspection methods, or training programs needed to insure product quality. Acceptance methods should be developed for accurate measurement of outgoing product quality.

Management Responsibility

As set forth by the QS regulation (820.20), one of the most important responsibilities of management when developing a quality system is to establish its policy and objectives for, and commitment to, quality. Management with executive responsibility shall ensure that the quality policy is understood, implemented, and maintained at all levels of the organization. This means each manufacturer shall establish the appropriate responsibility, authority, and interrelation of all personnel who manage, perform, and assess work affecting quality, and provide the independence and authority necessary to perform these tasks. The QS regulation also requires that each manufacturer shall establish and maintain an adequate organizational structure to ensure that devices are designed and produced in accordance with the GMP requirements. To meet these regulatory requirements, manufacturers are required to provide adequate resources, including the assignment of trained personnel for management, performance of work, and assessment activities, including internal quality audits.

Management with executive responsibility shall appoint a member of management who will have authority over and responsibility for:

- **Ensuring that quality system requirements are effectively established and effectively maintained; and**
- **Reporting the performance of the quality system to management with executive responsibility for review.**

Thus, the QS regulation requires that management with executive responsibility shall review the suitability and effectiveness of the quality system at defined intervals and with sufficient frequency according to established procedures to ensure that the quality system satisfies the regulatory requirements and the manufacturer's established quality policy and objectives. The dates and results of quality system reviews shall be documented.

The quality assurance personnel should be able to identify system problems, to recommend and provide solutions, and to verify implementation of the solutions. Other personnel may also identify and solve quality problems. The quality system should support such activities by all personnel. Feedback from quality assessment activities is necessary to verify the adequacy of the manufacturing process and the controls used. It also helps trigger corrective action to solve root causes of quality problems rather than just performing rework.

Typically, a quality system identifies problems with device quality through review of verification and validation data, inspection/test data, analysis of device history and service records, failure analysis, analysis of complaints, and review of other objective data. In this regard, reduction in productivity is often an indicator of quality problems. Low morale and confusion are indicators of inadequate procedures, and/or training and poor management. Also, measurement of scrap and rework is an effective method of detecting quality problems and reducing costs. These are examples of sources that provide feedback to the quality system.

In conclusion, each manufacturer is required to establish a quality plan which defines the quality practices, resources, and activities relevant to the devices that are designed and manufactured. The manufacturer shall establish how the requirements for quality will be met [820.20(d)]. Each manufacturer shall establish quality system procedures and instructions. To facilitate the understanding, use, review, and updating of the quality system, an outline of the structure of the documentation used in the quality system shall be established where appropriate [820.20(e)].

Formal and Documented Quality System

The QS regulation requires that each manufacturer prepare and implement quality system procedures adequate to assure that a formally established and documented quality system is implemented The system should include not only formal documentation, but also an obvious commitment to quality from top management. There should be manifest indications that management recognizes the need for a quality system in order to assure quality products. In many manufacturers, this commitment is accomplished through means such as: a management policy; assignment of responsibilities and authorities; and general statements and actions such as employee training that define goals of the quality system. This policy is supported by a number of more detailed quality system documents such as verification methods, sampling procedures, inspection/test procedures, product audits, and records indicating that measurement and monitoring of quality has occurred. The number of documents needed depends on the size and complexity of the operation and the characteristics of the product. The QS regulation requires the manufacturer to maintain various records such as:

- **design history files,**
- **device master records,**
- **device history records,**
- **maintenance schedules and records,**
- **complaint files and failed device/component files,**
- **audit reports,**
- **distribution records, and**
- **personnel training records.**

Most of these records are discussed in more detail in later chapters. In each case, the records should be appropriate for the device and the operation involved. Any changes to device master records should be made by a formal procedure and be formally approved.

Among other records, the device master record contains manufacturing procedures and standard operating procedures (SOP's). Some manufacturers tend to write an excessive number of general SOP's. Manufacturers should not generate and use procedures that are not needed. Also, standard operating procedures tend to not match actual operations because the operations gradually change as the company grows or as products are added without amending the procedures. Such procedures may require operations that have no benefit, or require excessive collection of data, or collection of data that is never used. Thus, manufacturers need to occasionally flow chart and analyze their operations to determine, among other things, if the existing procedures are inadequate, correct, or excessive. Flow-charting is a tool that directs a detailed audit of an operation. Flow-charting to analyze operations is an excellent method for improving operations and the associated quality system activities. At the end of Chapter 10, Purchasing and Acceptance Activities, an example of a flow-chart is contained in PA-1004, Procedure for Receiving and Inspection of Material, integral page 4 of 9.

Approval of Product

The quality system includes procedures for assuring that all products such as components, packaging, labeling, manufacturing materials, and finished devices have been approved for use; and

that contracted items and services are suitable [820.50, 820.80]. Likewise, the quality system shall assure that rejected items are identified and properly disposed [820.90]. Additionally, the quality system shall assure that production records are reviewed before the product is distributed [820.80(d)]. These records are part of the device history record. Device history records shall be reviewed to verify that the operations represented have been properly conducted and that the records are complete.

Quality Acceptance Activities

The quality system shall determine that all tests and inspections are performed correctly (see 820.80, 820.181, and 820.20). Some of the methods used to accomplish this are adequate test and inspection procedures, training of test personnel, quality system audits, review of quality system records, and product audits. However, simply instituting a quality system and checking that it is conducted correctly is not enough to satisfy the QS regulation. The regulation also requires that the quality system be appropriate and adequate for the purpose. This determination should be done during final product development, pilot production, and, of course, whenever product and/or processes are modified. In cases where conformance to specifications cannot be adequately measured by in-process or finished product testing and inspection, the system should include validation of processes.

Quality System Audits

The QS regulation requires (820.20) that each manufacturer shall prepare and implement quality system procedures adequate to assure that a formally established and documented quality system program is performed. Many activities are required to fulfill this requirement. As management performs their assigned routine duties, they should be aware of the obvious aspects of the quality system. However, to make sure that all aspects, obvious, hidden or subtle, of the required program exist and are operating correctly, the QS regulation requires planned and periodic audits (820.22) of the quality system. Management with executive responsibility reviews audit reports as part of their review of the suitability and effectiveness of the quality system.

Employee Training

QS regulation requires quality awareness training for manufacturing and quality system personnel [820.25(b)]. Personnel involved in quality system activities shall be properly trained, both by education and experience. No matter how effective quality system and production systems are as concepts, people still play the major role in producing a quality product. Lack of training -- as reflected in instances of negligence, poor operating techniques, or inability of employees to discharge their functions properly -- can lead to defective products and, sometimes, to regulatory or liability problems. Management should be diligent in looking for factors that indicate a need for employee training.

A quality system should include an ongoing formal program for training and motivating all personnel. All employees should be made aware that product quality is not solely the responsibility of management. Quality is the responsibility of every employee -- any employee can potentially generate a quality problem through negligence. It is extremely important to understand the following points with respect to typical quality-related functions.

- **Top management sets the quality attitude for the company.**

- **Research and development has primary responsibility for designing quality into the device.**

- **Technical services or an equivalent functional group has primary responsibility for documenting the design.**

- **Manufacturing, process or "scale-up" engineering has primary responsibility for designing quality into the manufacturing processes.**

- **Manufacturing personnel have primary responsibility for producing devices that have the maximum level of quality that can be achieved based on the product and process designs.**

- **Quality system personnel have primary responsibility for the program's management, status reports, audits, problem identification, data analysis, etc., as described in the QS regulation and in this manual.**

A medical device manufacturer should NEVER try to operate on the basis that only the quality system organization has primary and direct responsibility for the quality of the products. To do so means that quality problems will not be solved in a timely manner because attention is directed toward the wrong organization. In reality, it is part of the responsibility of the quality system to see that attention is directed toward the correct department if a quality problem arises.

Where necessary, employees should be certified to perform certain manufacturing or quality system procedures. Records of training and/or certification shall be maintained. Personnel performing quality system functions should:

- **have sufficient, well-defined responsibilities and authority;**
- **be afforded the organizational freedom to identify and evaluate quality problems;**
- **be able to formulate, obtain, and recommend possible solutions for quality system problems; and,**
- **verify implementation of solutions to quality problems.**

QUALITY SYSTEM MAINTENANCE

After the quality system is operational, personnel should continue to look for problem areas or factors that can have an impact on product quality. Many factors that can have an impact on product quality include:

- **changes in, or absence of, personnel;**

- **uncomfortable working conditions (e.g., breakdowns in air conditioning);**

- **increases in workload or production rates;**

- **introduction of new production or inspection equipment;**

- **changes in company incentive techniques (e.g., placing hourly employees on piecework can cause deterioration of product quality); and**

- **changes in sources for purchased components and materials, as well as changes in components, devices, or process techniques.**

As noted, quality system audits and flow-charting of operations are excellent methods for determining the detailed status of the system. Correcting problems or responding to conditions identified by audits, operational analyses, and customer feedback data can result in quality system improvements.

MEDICAL DEVICE REPORTING

FDA has promulgated regulations [803] for manufacturers, distributors, and initial distributor(s) requiring them to establish and maintain reports, including the Medical Device Reporting (MDR) reports for serious injuries, death, or certain other adverse incidents. If a manufacturer has a quality system as required by the QS regulation, the frequency of MDR reporting should be minimized.

3 DESIGN CONTROLS

INTRODUCTION

The Safe Medical Devices Act of 1990 added design validation requirements to the GMP requirements in section 520(f) of The Act. Section 820.30 of the Quality System (QS) regulation lists the design control requirements that manufacturers should satisfy to be in compliance. This chapter describes design controls and provides guidance to assist manufacturers in complying with design control requirements.

"Design Control Guidance for Medical Device Manufacturers" is another document that may assist manufacturers in understanding the intent of the design control requirements. This manual interprets the language of the QS regulation and explains the underlying concepts in practical terms. "Do It By Design: An Introduction to Human Factors in Medical Devices" is a document that

contains background information about human factors as a discipline, describes and illustrates device problems and discusses human factors principles and methods as a part of the design control system. Both of these manuals are possible resources for manufacturers who are either developing or improving their design control system. These manuals are also available through DSMA.

Coverage

The design controls section 820.30 of the QS regulation applies to the design of products, and processes and changes to existing designs and processes. Changes to existing designs should be made in accordance with design control requirement even if the original design was not subject to these requirements. Design controls are not retroactive to completed portions of ongoing design programs.

Each manufacturer of any class III or class II device, and class I devices automated with computer software and those listed below shall establish and maintain procedures to control the design of the device in order to make certain that specified design requirements are met. Manufacturers of other Class I devices should develop and document their devices under their own design control system because the documentation is needed to help meet the device master record requirements in 820.181 and marketing submission requirements. Thus, manufacturers of exempt Class I devices are encouraged to use 820.30, Design Controls, as guidance.

Classification Section	Class I Devices Subject to Design Controls Listed in Paragraph 820.30(a)(2)
868.6810	Catheter, Tracheobronchial Suction
878.4460	Glove, Surgeon's
880.6760	Restraint, Protective
892.5650	System, Applicator, Radionuclide, Manual
892.5740	Source, Radionuclide Teletherapy
All Sect.	Devices automated with computer software

The design requirements for the device are primarily specified by the manufacturer; however, FDA has a few design requirements in the 21 CFR Part 801 labeling regulations and in Parts 1000-1050 which cover radiological and electronic products. A few of the FDA design requirements are in standards. For example, some parameters for medical gloves are in standards by the American Society for Testing and Materials (ASTM). (That is, medical gloves are required to meet these standards in order to be substantially equivalent to gloves already in commercial distribution.)

QUALITY SYSTEM

Each manufacturer is required to establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured [820.5 and 820.1(a)(3)], and that meets the requirements of Part 820. Therefore, the details of design control systems will vary depending on the complexity of the product or process being designed. However, all non-exempt manufacturers including very small manufacturers and manufacturers that design less complex devices or processes are expected to define, document and implement design control procedures and other quality system procedures as called for in the regulation. One of these, a sample design input procedure, is exhibited at the end of this chapter.

Manufacturers may establish one design control procedure to cover the various design control sections in 820.30; or, they may use one or more procedures for each topic. Multiple procedures may be easier to develop, update and implement. Medium to large manufacturers may have several additional procedures to support their main design control procedures. Design control procedures may be part of the quality system records (QSR) noted in section 820.186.

Personnel Training

Personnel training in 820.25 is one of the quality system requirements, which applies to employees that perform any activity covered by the QS regulation including all design activities.

Manufacturers are required to establish procedures for identifying training needs and making certain that all personnel are trained to adequately perform their assigned responsibilities. Design personnel shall be made aware of device defects which may occur from the improper performance of their specific jobs. In particular, personnel who perform verification and validation activities shall be made aware of defects and errors that may be encountered as part of their job functions.

Most technical employees need various degrees of training, as appropriate, in the medical device regulations, safety, labeling, human factors, verification, validation, design review techniques, etc.

DESIGN AND DEVELOPMENT PLANNING

Developing a new device and introducing it into production are very complex tasks. For many new devices and associated manufacturing processes that use software, these tasks are further complicated because of the importance of software, and the possibility of subtle software errors. Without thorough planning, program control, and design reviews, these tasks are virtually impossible to accomplish without errors or leaving important aspects undone. The planning exercise and execution of the plans are complex because of the many areas and activities that should be covered. Some of the key activities are:

- **determining and meeting the user/patients requirements;**
- **meeting regulations and standards;**
- **developing specifications for the device;**
- **developing, selecting and evaluating components and suppliers;**
- **developing and approving labels and user instructions;**
- **developing packaging;**
- **developing specifications for manufacturing processes;**
- **verifying safety and performance of prototype and final devices;**
- **verifying compatibility with the environment and other devices;**
- **developing manufacturing facilities and utilities;**
- **developing and validating manufacturing processes;**
- **training employees;** • **documenting the details of the device design and processes; and,**
- **if applicable, developing a service program.**

To support thorough planning, the QS regulation requires each manufacturer to establish and maintain plans that describe or reference the design and development activities and define responsibility for implementation.

The plans should be consistent with the remainder of the design controls. For example, the design controls section of the quality system requires a design history file (DHF) [820.30(j)] that contains or references the records necessary to demonstrate that the design was developed in accordance with the:

1. **approved design plan, and**
2. **regulatory requirements.**

Thus, the design control plans should agree with, and require meeting, the quality system design control requirements. One of the first elements in each design plan should be how you plan to meet each of the design control requirements for the specific design you plan to develop; that is, the design plans should support all of the required design control activities. Such plans may reference the quality system procedures for design controls in order to reduce the amount of writing and to assure agreement.

Interface

Design And Development Planning section 820.30(b) states:

"The plans shall identify and describe the interfaces with different groups or activities that provide, or result in, input to the design and development process..."

If a specific design requires support by contractors such as developing molds, performing a special verification test, clinical trials, etc., then such activities should be included or referenced in the plan and proactively implemented in order to meet the interface and general quality system requirements. Of course, the interface and general requirements also apply to needed interaction with manufacturing, marketing, quality assurance, servicing or other internal functions.

Proactive interface is a important aspect of concurrent engineering. Concurrent engineering is the process of concurrently, to the maximum feasible extent, developing the product and the manufacturing processes. This valuable technique for reducing problems, cost reduction and time saving cannot work without proactive interface between all involved parties throughout all stages of the development and initial production program.

Structure of Plans

Each design control plan should be broad and complete rather than detailed and complete. The plan should include all major activities and assignments such as responsibility for developing and verifying the power supplies rather than detailing responsibility for selecting the power cords, fuseholders and transformers. Broad plans are:

- **easier to follow;**
- **contain less errors;**
- **have better agreement with the actual activities; and**
- **will require less updating than detailed plans.**

Over the years, several manufacturers have failed to follow this advice and opted for writing detailed design control procedures. They reported being unable to finish writing the over-detailed procedures and were unable to implement them.

Regardless of the effort in developing plans, they usually need updating as the development activities dictate. Thus, the QS regulation requires in 820.30(a) that the plans shall be reviewed, updated, and approved as the design and development evolves. The details of updating are left to the manufacturer; however, the design review meetings are a good time and place to consider, discuss and review changes that may need to be made in the design development plan.

DESIGN INPUT

Design input means the physical and performance requirements of a device that are used as a basis for device design [820.3(f)].

Section 820.30(c) Design Input, requires that each manufacturer shall establish and maintain procedures to make certain that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient. Also, a design requirement in 820.130 requires that each manufacturer shall make certain that device packaging and shipping containers are designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution. The intent of 820.130 is to add the broad conditions that are considered for a package design. Packaging design activities should be done according to design controls. Likewise, the design of the content and physical parameters of labeling are covered by design controls. Manufacturers that are exempt from design controls shall labeling and packaging specifications in the DMR (820.181) and are encouraged to use the QS design controls as guidance.

The input procedures shall address incomplete, ambiguous, or conflicting requirements. The design input requirements shall be documented and shall be reviewed and approved by a designated individual(s). The approval, including the date and signature of the individual(s) approving the requirements, shall be documented.

Under a design control system, manufacturers should identify device requirements during the design input phase or beginning of the design activity. Design input includes determining customer needs, expectations and requirements plus determining regulatory, standards, and other appropriate requirements. These various requirements are documented by the manufacturer in a set of device requirements. A set of design input requirements, when converted to engineering terminology, finalized and accepted as part of the device master record is called a device or product specification.

The design input phase usually is a continuum because intensive and formal input requirements activities usually occur near the beginning of the feasibility phase and continue to the early physical design activities. After the initial design input phase there are also intensive and formal activities to reduce the input requirements to engineering-type input specifications -- usually called a product or device specification.

At the opposite end of the design program, the last event is initial production which may be pilot production or the beginning of routine production. Whether a manufacturer starts with pilot or routine production depends on the nature of the new device and associated production. Pilot devices

may be distributed after design validation of initial units is completed if they meet all of the device master record and other GMP requirements. Some manufacturers, however, use the pilot models in training programs for technical writers, production and service personnel, etc. Pilot models are also commonly used in early marketing displays.

After the concept of the new device design is established, the following basic design input questions should have been answered:

1. **What is the real need for the new device?**
2. **Where will the new device be used?**
3. **Who will use the new device?**
4. **How will the new device be used?**
5. **With what devices will the new device be used?**
6. **How long will the new device be used? and**
7. **Other questions related to the specific device to be developed.**

Designing a device and verifying that it meets customer requirements are expensive and time consuming activities. Therefore, to control these activities and increase the probability of achieving desired safety and performance characteristics, device, software, and process requirements and specifications should be thoroughly reviewed and approved before physical design and development begins. As the design evolves, the hardware, software, packaging, labeling, etc., shall be verified [820.30(f)] and reviewed [820.30(e)] versus their latest specifications to verify that design input requirements have been met.

Input Checklists

Device requirements should identify all of the desired performance, physical, safety and compatibility characteristics of the proposed device and, ultimately, the finished device. Design input also includes requirements for labeling, packaging, manufacturing, installation, maintenance and servicing. The final device specifications should cover ALL of the device characteristics. The device specifications may incorporate other specifications by reference such as reference to the manufacturer's list of specifications for a type of device, to specific paragraphs in standards, or to all of a standard, etc. with respect to a referenced specification. It should be very clear exactly what is going to be met. A failure to properly address characteristics or factors such as immunity from transients in the power source, thermal stress, electromagnetic compatibility (EMC), packaging protection, shipping stability, proper maintenance, etc., can have disastrous consequences.

It is possible to diligently develop device requirements and still forget one or more elements in the final specification. Hopefully, no key factors will be left out. To reduce the probability of a requirement or characteristic being left out, a specification checklist(s) may be used during the design input phase. A checklist should be developed that is broad based but also germane to the product line of the manufacturer. If used, a checklist should be part of a standard operating procedure such as a Design Input Specification Procedure.

The input requirements should cover any standards that the manufacturer plans for the device to meet. In the United States, information about essentially all national and international standards may be obtained from the American National Standards Association (ANSI), 11 West 42nd Street, New York, New York, 10036, phone 212-642-4900. ANSI is a private organization, which monitors

most of the standards activity in the United States and foreign activity in which U.S. citizens "officially" participate. Thus, ANSI can supply addresses and other information about all well established standards writing groups. Also, ANSI has for sale many different types of standards including quality system standards. For example, the International Electrotech Commission has a draft design review standard, "Guide on Formal Design Review" (plus a supplement), which should be helpful to product assurance/design control personnel.

The QS regulation requires that the input procedures shall address incomplete, ambiguous, or conflicting requirements. Thus, every reasonable effort should made to collect all of the requirements from which the designers can generate detailed design specifications that are clear, correct and complete.

At the end of the major aspects of the design input stage, the design input requirements shall be documented and shall be reviewed and approved by a designated individual(s). The approval, including the date and signature of the individual(s) approving the requirements, shall be documented.

A documented device specification or set of specifications derived from the input requirements should exist at the beginning of the physical design project. The device and other related specifications should be kept current as the design of the device, packaging, labeling and manufacturing processes evolve during the development program. As the physical design evolves, the specifications usually become more specific and more detailed.

The device specification will undergo changes and reviews as the device design evolves. However, one goal of market research and initial design reviews is to establish complete device requirements and specifications that will minimize subsequent changes.

Old versions of the input requirements and later the input specifications are put in the design history file (DHF) or indexed in the computer as part of the DHF to help show that the design plan was followed.

DESIGN REVIEW

Design review [820.30(e)] is one of the key design control elements in a quality system. The objectives of design review are stated in the definition of design review in 820.3(h) as follows:

Design review means a documented, comprehensive, systematic examination of a design to evaluate the adequacy of the design requirements, to evaluate the capability of the design to meet these requirements, and to identify problems.

To meet the systematic design review requirement, device design and design reviews should progress through defined and planned phases starting with the design input phase and continuing through validation of initial production units or lots. Subsequent activities are usually design changes.

To meet the design review comprehensive requirement, assessments should include a formal review of the main device and subsystems, including accessories, components, software, labeling, and packaging; production and resource needs; and installation and service, if needed. The scope

includes performance, physical safety, compatibility with other devices, overall device system requirements, human factors, and environmental compatibility.

Even though users or medical practitioners will be aware of direct medical requirements, they may not be fully aware of physical safety, compatibility, system, human factors, and environmental requirements. Thus, the reviews of the design input and the design should extend beyond merely satisfying user-stated requirements in order to assure that safety and effectiveness goals are met.

As the development program progresses, the reviews should cover producibility and production documentation such as assembly drawings, manufacturing instructions, test specifications, test procedures, etc.

The extent and frequency of design reviews depends on the complexity and significance of the device being evaluated.

When the design program is a redesign of an existing device, a special effort should be made to assure that data obtained from previous failures, complaints, and service records are made available and reviewed by those responsible for design, design input and design review.

Combination Devices

Marketing submissions to FDA for drug delivery, drug coated, etc., devices are required to have appropriate data that supports combination claims. The verification of combination devices requires interaction between device, drug or other manufacturers. Records of this interaction, such as design review meeting minutes, are required in order to meet the interface requirements of 820.30(b), Design and Development Planning. The labeling and particularly the cross-labeling of combination devices should be carefully analyzed during verification and validation activities, and design review meetings.

Preparation For Reviews

The designated moderator or other designated employee should announce the formal review meetings with appropriate lead time and include an agenda.

Persons who are making presentations should prepare and distribute information to help clarify review issues and help expedite the review. However, the intent of the quality system is not that presentations be so formal and elaborate that designers are spending excessive time on presentations rather than on designing a safe and effective device.

Persons who plan to attend a review meeting should come prepared to discuss the key issues on the agenda and issues related to the current design phase. Design review meetings are a great educational forum. However, design review meetings should not be used as a primary tool to educate or bring new employees or unprepared employees up-to-speed. To do so detracts from the intent of the meeting and detracts from the intent of the GMP requirements. Obviously, design review is also an excellent educational tool. However, new, or new-to-the-project employees should be primarily oriented by other means that do not detract from the primary function of design review meetings.

Why Design Reviews

Design reviews are conducted for design definition, selection and adequacy; communication; and resolution of problems and issues. For example, the design review of the design input requirements and subsequent design input specifications for the device, labeling, packaging and accessories is performed to help select the best and/or needed characteristics and requirements, usually from among many available and sometimes conflicting inputs.

The design review of the initial requirements allows input from all parties. Various people may participate and "buy in" or "become part of the program." As the design input and review activities progress, any conflicts are resolved and the preliminary specifications for the device, accessories, labeling, and packaging are established. Herein, the device, accessories, labeling and packaging is called the device system. Because of the establishment of these input requirements and subsequent specifications, plus interface and communication during the reviews, all personnel are directed toward the goal of developing the "exact" same device system.

As the development progresses and the design and production processes evolve, design reviews reduce errors, help avoid problems, help find existing problems, help propose solutions, increase producibility and reduce production transfer problems. The relentless inquiry during design reviews will expose needed design input requirements and/or design corrections that otherwise may have been overlooked.

Throughout the design program and particularly toward the end of the development cycle, design reviews help assure that the final design of the device system meets the current design requirements and specifications.

Types Of Design Review Meetings

Design review meetings may be grouped into two levels such as:

- **total or major program review meetings, and**
- **sub-program or team review meetings.**

Some of the review meetings need to be total or major program review meetings because this is the only type of review meeting that will satisfy all of the GMP review requirements, particularly the interface requirement for interaction between or among different organizational groups. However, sub-program, team and contractor review meetings are design review meetings, are subject to quality system design controls, and should be conducted in a manner that meets the GMP requirements. Sub-program or team meetings are encouraged as these can be very effective and efficient in reviewing and resolving sub-program issues.

The records of total program and team meetings are part of the device design history file. The team review records or a summary of team records and the current design documentation are to be available, as appropriate, at total program review meetings.

Design review meetings are called under two scenarios:

- **first are the meetings that are preplanned and called at least on a per design phase;**

- **second are ad hoc meetings that are covered in the broad plans and are called to review or resolve a specific problem or issue.**

The preplanned design review meetings and ad hoc meetings are part of the planning and interaction that are required in 820.30(b), Design and Development Planning. That is, the manufacturer should expect, plan for, and encourage appropriate ad hoc meetings as well as the major design review meetings. Reasonable notes and copies of significant engineering documents discussed during total device system, ad hoc, contractor, and other review meetings are part of the device design history file.

Design Review Requirements

The objectives of design review are stated in the definition noted above. How these objectives are to be achieved are presented in the design review requirements. The main design review requirements are in 820.30(e) of the QS regulation as follows:

Each manufacturer shall establish and maintain procedures to ensure that formal documented reviews of the design results are planned and conducted at appropriate stages of the device's design development. The procedures shall ensure that participants at each design review include representatives of all functions concerned with the design stage being reviewed and an individual(s) who does not have direct responsibility for the design stage being reviewed, as well as any specialists needed. The results of a design review, including identification of the design, the date, and the individual(s) performing the review, shall be documented in the design history file.

There are four requirements related to design reviews:

1. **The meetings should be formal. That is, key attendees are designated and the meetings are conducted at least once per stage/phase, are planned, are announced or are periodic, have an appropriate agenda, notes are recorded, etc., according to the manufacturer procedure for design reviews.**

   The design review procedure should be broad and complete in that it contains information about all of the requirements. However, the procedure should not be so detailed that it cannot be followed. Over the years, several manufacturers have failed to follow this advice, tried to write detailed design QA procedures, and have reported that they were unable to finish writing the over-detailed procedures and were unable to implement them.

2. **To meet the definition of design review in 820.3(h), the review should include persons who are intimately knowledgeable about the technical characteristics of the design such as performance, safety, compatibility, etc. In many manufacturers this can only be done by those persons responsible for the design. However, reviews are to be objective, unbiased examinations by appropriately trained personnel which should include an individual(s) not responsible for the design. The moderator of the review meeting may be one of the persons not responsible for the design.**

   To meet interface and other review requirements, the review meetings should, as appropriate, include representatives of R&D, Engineering, Technical Support Services, Production Engineering, Manufacturing, Quality Assurance, Marketing, Installation and Servicing,

Purchasing and contractors. Design review should, as applicable and at the appropriate phase, include those responsible for coordinating or managing preclinical and clinical studies.

3. **Pre- and post-review meeting significant responsibilities and assignments should be documented [820.30(b)]. These assignments are not unusual -- they are simply ordinary work required to develop a new product or modify an existing product. The progress and/or results of such assignments would typically be reported at the next review meeting. Documentation is not required for detailed day-to-day development activities that are part of the designers routine job.**

4. **The design review meeting results are made a part of the device design history file. The results should include minutes and should include notes, or annotated draft drawings and annotated draft procedures that played a significant role during the design review. Such documents help show that plans were followed, verification/validation was reviewed, and, to some extent, how the design evolved.**

The QS regulation does not require that every document mentioned, referenced or used during a design review be placed in the design history file.

The device design review meeting minutes should include information such as:

- **moderator and attendees,**
- **date and design phase/stage,**
- **plans and/or agenda,**
- **problems and/or issues to identify and solve,**
- **minutes and reports, and**
- **follow-up report(s) of solutions and/or the next review covers the solutions and remaining issues.**

Manufacturers may use a form to capture some of this information for minutes such the device, date, moderator, attendees, major phase, problems, assignments, etc. The device design review minutes are a key and required part of the design history file. The minutes also help consolidate development information and the current minutes are also a brief record of some of the immediate development tasks to be done.

End Of Initial Design

The design control requirements, particularly design validation, give clear insight into when the initial dsign effort is completed. The end of the total design effort has not been reached until it is known that the initial production devices, when transferred to production and produced per the device master record, meet all of the current design specifications. This fact can only be determined by performing design validation on one or more samples of the finished production units as required by 820.30(g). Initial production and subsequent validation are well defined stages; and, therefore, design review(s) shall be performed as required by 820.30(e), Design Review.

Thus the design validation of initial production should be followed by a "final" design review to meet the design review requirement. If the validation of the final design and subsequent design review(s) reveal design problems, then design changes are required to correct these problems.

Design changes require another design verification and, where appropriate, validation and review of all parts or the affected parts of the device system.

DESIGN OUTPUT

Design output per 820.3(g) means the results of a design effort at each design phase and at the end of the total design effort. The finished design output is the basis for the device master record. The total finished design output consists of the device, its packaging and labeling, and the device master record.
Device master record (DMR) means a compilation of records containing the procedures and specifications for a finished device.

The design output at each phase are documents and physical design elements that are either complete or are used to move the design effort into the next phase. For example, the first design output will usually be the design requirements document. From the requirements and their engineering knowledge, the designers will derive the preliminary design specifications. Then the physical design begins. For example, the designers may begin the selection of known routine components that are part of the design and begin documenting their purchasing and acceptance requirements documented to meet 820.50 Purchasing Controls, (b) Purchasing Data which requires that each manufacturer shall establish and maintain data that clearly describe or reference the specified requirements, including quality requirements, for purchased or otherwise received product and services.

Other components will be selected as the design evolves. The design output for some special or new components, or components in unusual applications, will include verification protocols, purchasing and acceptance requirements.

Many of the design output documents are documents that directly form part of the DMR. The remaining DMR documents are created by quality assurance, production engineering, process engineering, technical writing, installation and servicing, etc., using design output data and information. For example, the finished device final-test methods and some installation and/or servicing test methods and data forms may be derived from the design verification protocol(s). When all of these design and documentation activities are completed, the DMR is complete. When the DMR is complete and initial production units, including packaging, meets all specifications, the total finished design output exists.

To generate the design output per the QS regulation in 820.30(d), three activities are required. Each of these is listed and discussed below.

1. **Each manufacturer shall establish and maintain procedures for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements.**

2. **Design output procedures shall contain or make reference to acceptance criteria and ensure that those design outputs that are essential for the proper functioning of the device are identified.**

3. **Design output shall be documented, reviewed, and approved before release. The approval, including the date and signature of the individual(s) approving the output, shall be documented.**

Documenting Design Output (1)

Documenting design output in terms that allow an adequate evaluation of conformance to design input requirements is a significant requirement and design activity. A common technique for achieving this conformance is listed below.

- **Convert the general input requirements to specific design engineering specifications and give each item a line/paragraph number.**

- **Develop the design to meet all of the parameters and characteristics in the design engineering specification.**

- **Generate a verification requirement document(s) and test method(s) for the design and give each requirement/parameter/characteristic the same line/paragraph number that it has in the design engineering specification.**

- **Generate a verification data form that lists each requirement/parameter/characteristic and give each requirement/parameter/characteristic the same line/paragraph number that it has in the design engineering specification.**

Each of these documents has a different drawing number but the line/paragraph numbers are the same. The first of these documents may be used as the beginning format for the next one. Therefore, it is almost impossible to leave out an element. Thereafter, when the verification is performed and documented, conformance or lack of conformance from input to output is known.

Acceptance Criteria (2)

The verification documents and data contain more information than is typically needed for production evaluation and acceptance of components, in-process items and finished devices. Therefore, it is easy to copy and modify verification documents to meet the quality system requirement that: design output procedures shall contain or make reference to acceptance criteria and ensure that those design outputs that are essential for the proper functioning of the device are identified. In fact, this technique of deriving test procedures from the verification protocols also yields the test method(s) and data form(s) needed to meet the DMR requirements for QA procedures and acceptance criteria in 820.181(c).

Design Output Approval (3)

The third and final output requirement is that: design output shall be documented, reviewed, and approved before release. The approval, including the date and signature of the individual(s) approving the output, shall be documented. This means that:

- **Manufacturers may choose to have a group review certain documents and have individuals review other documents.**

- **Output documents that are directly part of the DMR are reviewed, dated and signed by the author which is current practice; and reviewed, dated and approved by individual(s) designated by the manufacturer. As appropriate, these reviews should cover technical issues as well as adequacy for use in production, purchasing, servicing, etc. DMR documents that are generated and approved under 820.30 automatically meet the approval requirements of 820.40, *Document Controls* and do not have to be re-approved under 820.40.**

- **Design output reports, data and any other document that will be used to create documents in the DMR are reviewed, dated and signed by the author which is current practice; and reviewed, dated and approved by individual(s) designated by the manufacturer.**

Design output also includes the physical design which, of course, is not intended to be signed, and dated. The approval for the physical design is the validation that is done on initial production units.

DESIGN VERIFICATION AND VALIDATION

Each manufacturer shall establish and maintain procedures for verifying the device design. Design verification [820.30(f)] shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be documented in the DHF.

Validation [820.30(g)] means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

Process validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

Design validation means establishing by objective evidence that device specifications conform with user needs and intended use(s).

Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

Each manufacturer shall establish and maintain procedures for validating the device design. Design validation shall be performed under defined operating conditions on initial production units, lots, or batches, or their equivalents. Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions. Design validation shall include software validation and risk analysis, where appropriate. The results of the design validation, including identification of the design, method(s), the date, and the individual(s) performing the validation, shall be documented in the DHF.

Design verification is always done versus specifications. Therefore, to control the specifications and increase the probability of achieving desired safety and performance characteristics, device, software, labeling, packaging and any other specifications should be complete and thoroughly reviewed before development commences. As the hardware and software designs evolve, they should be evaluated versus their current specifications.

Verification and validation should be done with test equipment calibrated and controlled according to quality system requirements. Otherwise, there is limited confidence in the data.

Verification and validation should also be done according to a written protocol(s). The protocol(s) should include defined conditions for the testing. The protocol(s) should be approved before being used. Test protocol(s) are not perfect for a design, particularly a new design. Therefore, the designers and other verification personnel carefully annotate any ongoing changes to a protocol. Likewise, the verification personnel should record technical comments about any deviations or other events that occurred during the testing. The slightest problem should not be ignored. During design reviews, the comments, notes and deviations may be as important as test data from the formal protocol(s).

Design Evaluation versus Specifications

The original design of devices and any subsequent changes should be verified by appropriate and formal laboratory, animal, and in vitro testing. Risk analysis should be conducted to identify possible hazards associated with the design. Failure Mode Effects Analysis and Fault Tree Analysis are examples of risk analysis techniques.

Appropriate laboratory and animal testing followed by analysis of the results should be carefully performed before clinical testing or commercial distribution of the devices. The manufacturer should be assured that the design is safe and effective to the extent that can be determined by various scientific tests and analysis before clinical testing on humans or use by humans. For example, the electrical, thermal, mechanical, chemical, radiation, etc., safety of devices usually can be determined by laboratory tests.

Clinical testing is not needed for many substantially equivalent devices (See 21 CFR Part 807 Subpart E - Premarket Notification Procedure). Where it is needed, such as for complex substantially equivalent devices or new devices, clinical testing on humans should meet the applicable requirements in the Investigational Device Exemption (IDE) regulations (21 CFR Parts 812 and 813).

The general IDE regulation (21 CFR Part 812) exempts a manufacturer during the "premarketing phase" from the following provisions of the FD&C Act:

- **Misbranding,**
- **Registration of the Establishment,**
- **Premarket Notification [510(k)],**
- **FDA Performance Standards,**
- **Premarket Approval,**
- **Production sections ONLY of the Good Manufacturing Practices,**
- **Color Additives,**
- **Banned Devices, and**
- **Restricted Devices.**

Don't be misled by this list of exemptions -- being exempted from these provisions does not mean that a manufacturer may develop a new device under uncontrolled conditions and then test it on humans. Devices being clinically tested are not exempt from section 501(c) of the FD&C Act, which

states that a device is adulterated if it does not meet a manufacturer's quality claims. Devices being manufactured for use in clinical studies under an IDE are exempt ONLY from the production section of the QS regulation. They are not exempt from design controls listed in 820.30. In addition, the IDE regulation has labeling requirements in 812.5 and quality assurance requirements in 812.20(b)(3) that shall be met. Further, manufacturers should remember that human subjects are also protected through the courts via product liability laws and actions. In summation, protection of manufacturer interests, human test subjects, practitioners, and patients requires that all medical devices be developed, evaluated, and manufactured under a total quality system.

Laboratory testing to force a failure takes considerable time and the "culprit" may not fail during the testing. Another evaluation technique is Failure Mode and Effects Analysis (FMEA) in which failures are assumed to occur. FMEA is useful for evaluating reliability, safety, and general quality where, for example, the evaluator assumes that:

- **each component fails,**
- **each subsystem or subassembly fails,**
- **the operator makes errors, and**
- **the power source is interrupted and immediately restarted.**

The probability of each failure actually occurring and, if it does, the resulting effect are analyzed. Then, where needed and feasible, hazards and faulty performance are designed out of the device or reduced; or compensated or prevented/reduced by interlocks, warning signs, explicit instructions, alarms, etc. Risks, of course, cannot always be removed from medical devices, but they should be known and controlled to the extent feasible with existing technology.

Failure Mode and Effects Analysis (FMEA) is a very powerful and cost-effective technique. Note that it takes very little time to assume that a component or subsystem is going to fail versus the time required to test to failure. The idea is not to promote one method above the other because a reasonable amount of both actual testing and failure mode and effects analysis should be done before a device is clinically tested and/or placed into production.

Besides using FMEA there are also other human factor and validation process techniques that can be used in developing an overall risk analysis. These techniques include: timelines, workload analysis, failure analysis, alternative calculations, testing including animal testing, auditing the design output, design reviews, demonstrations, and comparing a new design to a proven design etc. The users should be considered components when developing a fault tree and failure mode effects analysis.

All evaluation results should be reviewed by product development personnel who compare the tests and FMEA results with specifications, including safety and performance standards, to make certain that the desired level of intrinsic quality has been designed into the device. Also, the appropriate design of manufacturing processes, including validation where appropriate, is needed to assure that production can achieve the level of quality designed into the device.

Software Validation

Software is evaluated and reviewed versus the software specifications during the ongoing development of the device design. When a "final" prototype(s) is available, the software and hardware are validated to make certain manufacturer specifications for the device and process are

met. Some aspects of hardware evaluation were discussed above. Aspects specific to software are covered below.

Before testing the software in actual use, the detailed code should be visually reviewed versus flow charts and specifications. All cases, especially decision points and error/limit handling, should be reviewed and the results documented.

In all cases, algorithms should be checked for accuracy. Recalls have occurred because algorithms were incorrectly copied from a source and, in other cases, because the source algorithm was incorrect. During the development phase, complex algorithms may need to be checked by using a test subroutine program written in a high-order language, if the operational program is written in a low-level language.

The validation program is planned and executed such that all relevant elements of the software and hardware are exercised and evaluated. The testing of software usually involves the use of an emulator and should include testing of the software in the finished device.

The testing includes normal operation of the complete device; and this phase of the validation program may be completed first to make certain that the device meets the fundamental performance, safety and labeling specifications. Concurrently or afterward, the combined system of hardware and software should be challenged with abnormal inputs and conditions. As appropriate, these inputs and conditions include such items as:

- **operator errors;**
- **induced failure of sensors and cables or other interconnects;**
- **induced failure of output equipment;**
- **exposure to static electricity;**
- **power loss and restart;**
- **simultaneous inputs or interrupts; and,**
- **as appropriate, deliberate application of none, low, high, positive, negative, and extremely high input values.**

The results of the software and combined device system validation are included in the design reviews.

Labeling Verification

During verification, the complete device is exercised such that all labeling, displays, and outputs are generated, reviewed, and the results documented. During the verification, all displayed prompts and instructions are checked versus the manufacturer's and FDA's labeling requirements and versus the operator manual.

Printed labeling and screen displays should be checked to see if they are directed to the user and not to the system designers, which is a common fault found in labeling. Displayed text should be short and to the point. Because displays are brief, keywords should be carefully selected to match system characteristics, yet transfer the maximum information to the user. The text of references to controls or other parts of the system should match the labeling on the device. Data, identifications, or other key information displayed should be current, complete, unambiguous, and accurate.

During verification, all prompts and instructions should be followed exactly by the device test or other operators and such action should result in correct operation of the device. Prompts and instructions should appropriately match the instructions in the operator's manual. The evaluation should include verification that any screen or other displays meet the requirements of, and have been approved per, the manufacturer's policy/procedure for design of labeling.

Patient and procedure data on printouts should be correct; therefore, printouts should undergo a verification similar to that performed for the screen or other displays. In addition, the printouts should be evaluated with respect to their "cold" information transfer characteristics. Will the printouts be quickly and clearly understood a few weeks later when the reader is not reading the displays, operating the device, or looking at the patient? All printouts should also meet the manufacturer's design control policy/procedure requirements for labeling. Likewise, patient data or other key information transmitted to a remote location should be correct; therefore, it should be checked for accuracy, completeness, and identification. Annotated copies of verified labeling, printouts, etc. and associated notes and any checklists should be placed in the design history file.

The overall device specifications usually have requirements that cover user/operator error prevention and control. Along with operator training, such errors are controlled by:

- **adequate instruction manuals,**
- **adequate device labels,**
- **display of adequate prompts and correct instructions,**
- **status (history) reports,**
- **exclusion of certain erroneous inputs or actions, and**
- **adequate human factors design.**

Also, for some devices, it may be important to control the order in which data can be entered by the operator. In emergency situations or because of distractions, it may be important to present the operator with a brief history or status report of recent actions. During the verification, the listed items should be evaluated versus the specifications, and checked for completeness and appropriateness. A checklist or matrix may be used to aid in the review of labeling.

DESIGN TRANSFER

The design controls require that each manufacturer shall establish and maintain procedures to ensure
that the device design is correctly translated into production specifications.

It is common practice for sections of a design to be transferred before the entire design is completed. The QS regulation does not prevent such split or multiple transfers. Transfer is to be performed only for completed elements of the design -- multiple transfers may not be used to bypass any design, labeling or other GMP requirements.

A significant part of the transfer requirement is met when the design output is being created. That is, some of the design output documents are part of the DMR and are used directly for production. The remaining DMR documents are based on design output information. A procedure is needed to cover the generation of the remaining device master record documents based on information in the design output documents.

Design transfer should assure that the section of the design being transferred:

- **meets input requirements;**
- **contains acceptance criteria, where needed;**
- **contains design parameters which have been appropriately verified;**
- **is complete and approved for use;**
- **is fully documented in the DMR or contains sufficient design output information to support the generation of remaining DMR documents; and**
- **is placed under change control if not already done.**

Design transfer may include training of production, installation and service employees and such training should be covered by or referenced by the transfer procedure.

DESIGN CHANGES

Changes to a design element are controlled per 820.30(i) *Design Changes* which states that: each manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation.

The original design activities and subsequent change control activities for the design are both done under the full set of the quality system design controls. A manufacturer may not use a design change control procedure to bypass part of the design controls. Thus, it is difficult to describe change control before design transfer because both activities are done under design controls.

Most of the details of the change control system are left to the manufacturer to develop, document and implement. As the design activity progresses toward the final stage, it is expected that the degree of change control will increase.

Those elements of the design that have been verified and accepted obviously should be under change control. A design that has been submitted to FDA for marketing clearance should be under change control. A design undergoing clinical trials should be under change control or the clinical data may not be accepted by FDA. A design that is released for production should be under design and general change control.

After design activities are begun and the physical design evolves into an accepted entity, subsequent changes to the device specification(s) are proposed, evaluated, reviewed, approved, and documented per all of 820.30. The revised specification(s) becomes the current design goal in accordance with the manufacturer procedures for: design control, design change control, and document control.

A design change control procedure should at least cover:

- **under what conditions change control is required;**

- **documenting the reason for the change;**

- **any differences in the change control process when outside parties are involved;**

- **analysis of the design to identify other elements that are impacted by the change; and**

- **for significant changes which includes any change requiring verification and/or validation, placing the reason for the change in the design history file along with the required design verification, validation and review documentation.**

DESIGN HISTORY FILE

Design history file (DHF) means a compilation of records which describes the design history of a finished device [820.3(e)].

The DHF covers the design activities used to develop the device, accessories, major components, labeling, packaging and production processes.

The design controls in 820.30(j) require that each manufacturer shall establish and maintain a DHF for each type of device. Each type of device means a device or family of devices that are manufactured according to one DMR. That is, if the variations in the family of devices are simple enough that they can be handled by minor variations on the drawings, then only one DMR exists. It is common practice to identify device variations on drawings by dash numbers. For this case, only one DHF could exist because only one set of related design documentation exists. Documents are never created just to go into the DHF.

The QS regulation also requires that the DHF shall contain or reference the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of this part. As noted, this requirement cannot be met unless the manufacturer develops and maintains plans that meet the design control requirements. The plans and subsequent updates should be part of the DHF. In addition, the QS regulation specifically requires that:

- **the results of a design review, including identification of the design, the date, and the individual(s) performing the review, shall be documented in the DHF.**

- **design verification shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be documented in the DHF.**

Typical documents that may be in, or referenced in, a DHF are listed below:

- **design plans;**
- **design review meeting information;**
- **sketches;**
- **drawings;**
- **procedures;**
- **photos;**
- **engineering notebooks;**
- **component qualification information;**
- **biocompatibility (verification) protocols and data;**
- **design review notes;**
- **verification protocols and data for evaluating prototypes;**
- **validation protocols and data for initial finished devices;**
- **contractor / consultants information;**
- **parts of design output/DMR documents that show plans were followed; and**
- **parts of design output/DMR documents that show specifications were met.**

The DHF contains documents such as the design plans and input requirements, preliminary input specs, validation data and preliminary versions of key DMR documents. These are needed to show that plans were created, followed and specifications were met.

The DHF is not required to contain all design documents or to contain the DMR, however, it will contain historical versions of key DMR documents that show how the design evolved.

Does the DHF have value for the manufacturer? Yes, when problems occur during re-design and for new designs, the DHF has the "institutional" memory of previous design activities. The DHF also contains valuable verification and validation protocols that are not in DMR. This information may be very valuable in helping to solve a problem; pointing to the correct direction to solve a problem; or, most important, preventing the manufacturer from repeating an already tried and found-to-be-useless design.

EXHIBITS

Design Input Requirements Procedure

A sample Design Input Requirements procedure is presented which covers basic activities for obtaining data on requirements that is needed for employees to develop device specifications. This procedure uses the multiple specification approach; however, a single combined specification would

use a very similar procedure. This procedure should be modified to meet specific needs before being adopted by a manufacturer.

C O M P A N Y L O G O

Title: Design Input Requirements Procedure **SOP #:** **Page: 1 of 2**

Prepared by: **App:** **Date:**

Prep. Date: **Rev:** **Date:**

ECN History:

POLICY - Design specifications covering all design requirements shall be established for all proposed devices before any significant physical design activities are started.

SCOPE - This policy applies to all devices and accessories developed by the manufacturer or developed by a contractor for us. For purchase of completed designs, refer to SOP ####. The device specification(s) must exist or be generated regardless of the source of the design.

CONFIDENTIALITY - Device development plans and activities are always confidential. Market research reports and documents such as specifications with parameter data shall be marked confidential.

Design control procedures, standard SOPs, blank forms, and required design review and design verification/validation records may be shown to, and may be copied by, FDA investigators as required by the QS regulation. Design parameters are not covered by the QS regulation. Therefore, confidential specification characteristics and parameters in the copies of these documents shall be blacked out unless the document is being collected during an inspection related to a marketing submission.

RESPONSIBILITY

Marketing and Engineering have the primary responsibility for determining safety and performance requirements and developing input specifications; however, all departments are expected to support the development of input requirements and subsequent specifications.

MARKETING - Marketing shall plan and conduct all customer contacts to obtain information on customer desires, needs, expected pricing, opinions about existing devices, etc.

To the maximum extent feasible, market research shall be conducted in a manner to reduce leaking of manufacturer confidential information and plans.

Design review meetings shall normally precede and follow all significant outside market research activities. Initial market research activities shall be previewed with top management.

Market research results are to be documented and marked confidential.

PRODUCTION - Production has primary responsibility for assuring producibility and establishing manufacturing requirements. Some of these requirements may be general during the early design stages.

ENGINEERING - Engineering is expected to supply design input information on most requirements. Such inputs may parallel data obtained by market research.

Engineering has primary responsibility for specifying what technology to use.
Engineering shall analyze input data on requirements and reduce it to preliminary specifications.
Engineering has primary responsibility for addressing incomplete, ambiguous, or conflicting requirements and shall see that such issues are appropriately discussed at design reviews.

RA & QA - RA and QA managers or their designees shall attend all design input or specification review meetings to provide input on, and to assure that, regulatory, manufacturer, quality, safety, performance, etc., procedures are followed and that requirements are met.

SPECIFICATIONS

STRUCTURE - Multiple specifications shall be used except for very simple devices. A separate specification shall be developed for accessories, labeling, packaging, etc. An overall device specification shall be developed and shall include an index that points to supporting specifications. The specifications, among other factors, shall address:

1. **Performance and Efficacy;**
2. **Human Factors;**
3. **Chemical Safety;**
4. **Electrical Safety;**
5. **Mechanical Safety;**
6. **Radiation Safety;**
7. **Thermal Safety;**
8. **Biocompatibility;**
9. **Device Compatibility;**
10. **System Compatibility;**
11. **Environmental Compatibility;**
12. **Packaging (in a separate specification document);**
13. **Any FDA design requirements in the Part 801 and Part 1000-1050 regulations; and**
14. **Labeling in a separate document and, as appropriate, in the device primary specification.**

CHECKLISTS - Checklists of requirements germane to our product line may be used to develop and support specifications. If used, such checklists become part of this procedure and part of the design documentation.

DESIGN REVIEW - Each specification shall undergo design review before it is approved for physical design activities or is used as a background document to support further market research. Such reviews shall be documented.

APPROVAL - The Marketing manager and Engineering manager shall approve all input specifications after these have been subjected to design review.

DOCUMENTATION - The approved specifications shall be given document numbers and become part of the device master record for the new device.

CHANGE CONTROL - The Engineering manager shall decide when design activities have progressed to the stage that the various specifications shall be subject to our Design Change Control Procedure. However, for our organization, design change control can start NO later than the FIRST of the following events:

- **clearance of a 510(k), or**
- **start of a clinical investigation.**

4 PROCESS VALIDATION

INTRODUCTION

The Quality System (QS) regulation defines process validation as establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications [820.3(z)(1)]. The requirement for process validation appears in section 820.75 of the Quality System (QS) regulation. The goal of a quality system is to consistently produce products that are fit for their intended use. Process validation is a key element in assuring that these principles and goals are met.

The process validation requirements stated in the QS regulation and the guidance offered here have general applicability to manufacturing processes for medical devices. Many technologies are used in the production of medical devices. The details of process validation will vary according to the nature of the medical device (e.g., sterile or non-sterile) and the nature and complexity of the process being validated.

Processes are developed according to the design controls in 820.30 and validated according to 820.75. The process specifications, hereafter called parameters, are derived from the specifications for the device, component or other entity to be produced by the process. The parameters are documented in the device master record per 820.30, 820.40 and 820.181. The process is developed such that the required parameters are achieved. To ensure that the output of the process will consistently meet the required parameters during routine production, the process is validated.

The basic principles for validation may be stated as follows:

- **Establish that the process equipment has the capability of operating within required parameters;**

- **Demonstrate that controlling, monitoring, and/or measuring equipment and instrumentation are capable of operating within the parameters prescribed for the process equipment;**

- **Perform replicate cycles (runs) representing the required operational range of the equipment to demonstrate that the processes have been operated within the prescribed parameters for the process and that the output or product consistently meets predetermined specifications for quality and function; and**

- **Monitor the validated process during routine operation. As needed, requalify and recertify the equipment.**

TERMS AND DEFINITIONS

Terms other than those used herein may be found in the literature.

Validation: confirmation by examination and provision of objective evidence that the particular requirement for a specific intended use can be consistently fulfilled.

Process validation: establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

Installation qualification: establishing documented evidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances.

Process performance qualification: establishing documented evidence that the process is effective and reproducible.

Product performance qualification: establishing documented evidence through appropriate testing that the finished product produced by a specified process(es) meets all release requirements for functionality and safety.

Prospective validation: validation conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product's characteristics.

Retrospective validation: validation of a process for a product already in distribution based upon accumulated production, testing and control data.

Validation protocol: a written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results.

WHY VALIDATE PROCESSES

There are many reasons, in addition to the regulatory requirements, for validating processes. A manufacturer can assure through careful design of the device and packaging, careful design and validation of processes, and process controls, that there is a high probability that all manufactured

units will meet specifications and have uniform quality. The dependence on intensive in-process and finished device testing can be reduced. However, in-process and finished product testing still play an important role in assuring that products meet specifications. A properly validated and controlled process will yield little scrap or rework, resulting in increased output. Consistent conformance to specifications is likely to result in fewer complaints and recalls. Also, when needed, the validation files contain data to support improvements in the process or the development of the next generation of the process.

WHAT PROCESSES SHOULD BE VALIDATED

Where process results cannot be fully verified during routine production by inspection and test, the process must be validated according to established procedures [820.75(a)]. When any of the conditions listed below exist, process validation is the only practical means for assuring that processes will consistently produce devices that meet their predetermined specifications:

- **Routine end-product tests have insufficient sensitivity to verify the desired safety and efficacy of the finished devices;**
- **Clinical or destructive testing would be required to show that the manufacturing process has produced the desired result or product[1];**
- **Routine end-product tests do not reveal all variations in safety and efficacy that may occur in the finished devices[2];**
- **The process capability is unknown, or it is suspected that the process is barely capable of meeting the device specifications.**

TYPES OF PROCESS VALIDATION

Process validation may be conducted at different points during the life cycle of a product. The types of process validation are defined in terms of when they occur in relation to product design, transfer to production and release of the product for distribution.

Prospective Validation

Prospective validation is conducted before a new product is released for distribution or, where the revisions may affect the product's characteristics, before a product made under a revised manufacturing process is released for distribution.

Concurrent validation is a subset of prospective validation and is conducted with the intention of ultimately distributing product manufactured during the validation study. Concurrent validation is

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[1] For example, USP 23 states: "Absolute sterility cannot be practically demonstrated without complete destruction of every finished article."

[Added note: Also, a positive test result may be caused by operator error rather than non sterility.]

[2] For example, visual inspections usually are not capable of detecting defects in structural welds. Such defects may be detectable only by using destructive testing, expensive test equipment, or very slow test methods.

feasible when nondestructive testing is adequate to verify that products meet predetermined specifications and quality attributes. If concurrent validation is being conducted as the initial validation of a new process or a process which has been modified, product should be withheld from distribution until all data and results of the validation study have been reviewed, and it has been determined that the process has been adequately validated.

Concurrent validation may be conducted on a previously validated process to confirm that the process is validated. If there have been no changes to the process and no indications that the process is not operating in a state of control, product could be released for distribution before revalidation of the process is completed. There is some risk to early release of product in that subsequent analysis of data may show that the process is not validated.

Retrospective Validation

Retrospective validation is the validation of a process based on accumulated historical production, testing, control, and other information for a product already in production and distribution. This type of validation makes use of historical data and information which may be found in batch records, production log books, lot records, control charts, test and inspection results, customer complaints or lack of complaints, field failure reports, service reports, and audit reports. Historical data must contain enough information to provide an in-depth picture of how the process has been operating and whether the product has consistently met its specifications. Retrospective validation may not be feasible if all the appropriate data was not collected, or appropriate data was not collected in a manner which allows adequate analysis.

Incomplete information mitigates against conducting a successful retrospective validation. Some examples of incomplete information are:

- **Customer complaints which have not been fully investigated to determine the cause of the problem, including the identification of complaints that are due to process failures;**
- **Complaints were investigated but corrective action was not taken;**
- **Scrap and rework decisions that are not recorded, investigated and/or explained;**
- **Excessive rework;**
- **Records that do not show the degree of process variability and/or whether process variability is within the range of variation that is normal for that process, for example, recording test results as "pass" or "fail" instead of recording actual readings or measurements results in the loss of important data on process variability; and**
- **Gaps in batch records for which there are no explanations. (Retrospective validation cannot be initiated until the gaps in records can be filled or explained.)**

If historical data is determined to be adequate and representative, an analysis can be conducted to determine whether the process has been operating in a state of control and has consistently produced product which meets its predetermined specifications and quality attributes. The analysis must be documented.

After a validated process has been operating for some time, retrospective validation can be successfully used to confirm continued validation of that process if no significant changes have been made to the process, components, or raw materials.

Statistical process control is a valuable tool for generating the type of data needed for retrospective analysis to revalidate a process and show that it continues to operate in a state of control.

PROCESS VALIDATION STUDIES

Planning the Process Validation Study

Careful planning of a validation study is essential to ensure that the process is adequately validated. The plan should include design reviews. The plan for the validation study is documented in the validation protocol. A copy of the protocol and validation results are placed in the Design History File (DHF) [820.30 (j)] or quality system record file (820.186). The operational, monitoring, and other production-related procedures are part of the device master record (DMR) (820.181). Planning for the validation should include the following elements as well as any other relevant issues that must be addressed to conduct the validation study:

- **identification of the process to be validated;**
- **identification of device(s) to be manufactured using this process;**
- **criteria for a successful study;**
- **length and duration of the study;**
- **assumptions (shifts, operators, equipment, components);**
- **identification of equipment to be used in the process [820.75(b)(2)];**
- **identification of utilities for the process equipment and quality of the utilities;**
- **identification of operators and required operator qualifications [820.75(b)(2)];**
- **complete description of the process {may reference the DMR [820.181(b)]};**
- **relevant specifications including those for the product, components, manufacturing materials, the environment, etc. [may reference the DMR and quality system files {820.181(a) and (b); 820.186};**
- **any special controls or conditions to be placed on preceding processes during the validation;**
- **process parameters to be controlled and monitored, and methods for controlling and monitoring [820.70(a); 820.75(b)(2)];**

- **product characteristics to be monitored and method for monitoring [820.70(a)(2); 820.75(b)(2); 820.80(c)];**
- **any subjective criteria used to evaluate the product;**
- **definition of what constitutes nonconformance for both measurable and subjective criteria;**
- **statistical methods for data collection and analysis (820.250);**
- **consideration of maintenance and repairs [820.72(a)];**
- **conditions that may indicate that the process should be revalidated [820.75(c)];**
- **stages of the study where design review is required; and**
- **approval(s) of the protocol.**

The validation plan should also cover the installation and operation qualification of any equipment used in the process, process performance qualification, and product performance qualification.

Installation and Operation Qualification

After process equipment is designed or selected, it should be installed, reviewed, calibrated, challenged, and evaluated to ensure that it is capable of operating within established limits and tolerances as well as throughout all anticipated operating ranges. Installation and operation qualification studies establish confidence that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use [820.70(g)].

The installation and operation qualification phases of process validation include:

- **examining equipment design and supplied documentation;**
- **determining installation requirements;**
- **establishing any needed environmental controls and procedures;**
- **assuring that the work area has sufficient space to perform the processing and associated activities;**
- **installing the equipment;**
- **verifying correct installation;**
- **establishing manufacturing procedures for the monitoring, operation, and control of the equipment including the minimum number of operators;**

- **determining calibration, cleaning, maintenance, adjustment, and expected repair requirements;**

- **identifying important elements of the equipment that could affect the output or finished device;**

- **verifying that the system or subsystem performs as intended throughout all anticipated operating ranges; and**

- **documenting the above information.**

Equipment fabricators may perform qualification runs at their facilities and analyze the results to determine that the process equipment is ready for delivery to the medical device manufacturer. Device manufacturers should obtain copies of the suppliers' qualifications studies to use as guides, to obtain basic data, and to supplement their own qualification studies. However, it is usually insufficient to rely solely upon the representations and studies of the equipment supplier. The device manufacturer is ultimately responsible for evaluating, challenging, and testing the equipment and deciding whether the equipment is suitable for use in the manufacture of a specific device(s). The evaluations may result in changes to the equipment or process. Such changes must meet QS requirements in 820.30, Design Control; 820.40, Document Controls; 820.50, Purchasing Controls; 820.70, Process Controls; 820.72, Inspection, Measuring, and Test Equipment; 820.75, Process Validation; 820.181, Device Master Record.

Installation and operation qualifications should include establishing pertinent methods, procedures, and schedules for calibration, cleaning, and maintenance, and establishing a repair parts list for each piece of equipment. Planning for eventual maintenance and repairs can reduce or prevent confusion during emergency repairs which could lead to improper repairs such as the use of the wrong replacement part. Post-repair cleaning, calibration, and re-start requirements should be established if necessary to prevent inadvertent manufacture of nonconforming devices. The objective is to assure that all repairs can be performed in a way that will not affect the characteristics of material processed or devices manufactured after repairs.

Process and monitoring equipment (instruments) should be calibrated at the beginning of the validation study, and the calibration should be checked at the end of the study to establish confidence in the validation of the process. Equipment found out of calibration at the end of a process validation study may indicate that the process has not been operating in a state of control and cannot be considered validated. More frequent calibration or more robust equipment may be necessary, or you may wish to use stand-alone instruments in parallel with the built-in process monitoring equipment.

It is important to document installation and operation qualification studies. Such documentation can substitute for part of the requalification of equipment in future process validation studies. When equipment is moved to a new location, installation and operation should be requalified. By comparing data from the original installation and operation qualification and the requalification, the manufacturer can determine whether there have been any changes in equipment performance as a result of the move. Changes in equipment performance should be evaluated to determine whether it is necessary to revalidate the process.

Process Performance Qualification

The purpose of *process* performance qualification is to rigorously test the process to determine whether it is capable of consistently producing an output or in-process or finished devices which meet specifications. In entering the process performance qualification phase of validation, it is understood that the:

- **device, packaging, and process specifications have been established, documented, and essentially proven acceptable through engineering, laboratory or other verification methods [820.30; 820.70(a)]; and**

- **process and ancillary equipment and the environment have been judged acceptable on the basis of installation and operation qualification studies [820.70(g)].**

Challenges to the process should simulate conditions that will be encountered during actual production. Challenges should include the range of conditions allowed in written standard operating procedures and should be repeated enough times to assure that the results are meaningful and consistent. Challenges may need to include forcing the preceding process to operate at its allowed upper and lower limits.

Process and product data should be analyzed to determine what the normal range of variation is for the process output. Knowing what is the normal variation of the output is crucial in determining whether a process is operating in a state of control and is capable of consistently producing the specified output.

Process and product data should also be analyzed to identify any variation due to controllable causes. Depending on the nature of the process and its sensitivity, controllable causes of variation may include:

- **temperature,**
- **humidity,**
- **variations in electrical supply,**
- **vibration,**
- **environmental contaminants,**
- **purity of process water,**
- **light, and**
- **inadequate employee training.**

Appropriate measures should be taken to eliminate controllable causes of variation. For example, extreme variations in temperature can be eliminated by installing heating and air conditioning. Employee training can be improved and conducted more frequently, and employees can be monitored more closely to assure that they are properly performing the process. Eliminating controllable causes of variation will reduce variation in the process output and result in a higher degree of assurance that the output will consistently meet specifications.

After routine production begins, data derived from monitoring the process and output product can be analyzed for variation and compared to the normal range of variation. Such analyses can detect when the process output is shifting so that corrections can be made before, or soon after, nonconforming product is produced.

Product Performance Qualification

The purpose of *product* performance qualification is to demonstrate that the process has not adversely affected the finished product and that the product meets its predetermined specifications and quality attributes. Product performance qualification and design validation of initial finished devices are closely related. According to the design control requirements, design validation shall be performed under defined operating conditions on initial production units, lots, or batches, or their equivalents [820.30(g)]. Products used for design validation should be manufactured using the same production equipment, methods and procedures that will be used in routine production. Otherwise, the product used for design validation may not be representative of production units and cannot be used as evidence that the manufacturing process will produce a product that meets pre-determined specifications and quality attributes.

Design validation can be conducted using finished products made during process validation studies and will satisfy the need for product performance qualification. Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing production units under actual or simulated use conditions [820.30(g)]. Original designs and design changes are subject to design control requirements [820.30(i)]. The results of design validation are subject to review under the design control review requirements [820.30(e)].

DOCUMENTATION

The requirements for process validation are described in section 820.75 and include documentation requirements for the process validation study phase as well as for routine production using a validated process. Records of validation activities and results must be maintained [820.75(a)]. Validation protocols and results may be filed in the DHF [820.30(j)] or in the QS files (820.186). Records must include the date and signature of the individual(s) approving the validation and, where appropriate, the major equipment validated [820.75(a)]. Procedures for monitoring and control of process parameters must be established and maintained for validated processes [820.75(b)]. Procedures for the operation, monitoring and control of processes are part of the DMR (820.181).

When a validated process is used for manufacturing finished devices, the process must be performed by a qualified individual [820.75(b)(1)]. Records must be maintained of the monitoring and control methods and data; where appropriate, the individual(s) performing the process; the date performed; and major equipment used. The records should be maintained in the DHR (820.184).

REVALIDATION

As long as the process operates in a state of control and no changes have been made to the process or output product, the process does not have to be revalidated. Whether the process is operating in a state of control is determined by analyzing day-to-day process control data and any finished device testing data for conformance with specifications and for variability.

When changes or process deviations occur, the process must be reviewed and evaluated, and revalidation must be performed where appropriate [820.75(c)]. Review, evaluation, and revalidation activities must be documented.

Processes may be routinely validated on a periodic basis; however, periodic validation may not be adequate. More important is appropriate monitoring so that if problems develop or changes are made, the need for immediate revalidation is considered.

REFERENCES

1. Guideline on General Principles of Process Validation, May 1987, FDA, CDRH/CDER
2. Journal of Validation Technology, Vol. 1, No. 4, August 1995

5 PERSONNEL AND TRAINING

INTRODUCTION

Establishing a quality system should be an integrated and universal effort. A total quality systems approach should be designed to satisfy the particular quality, safety, and performance needs of a specific manufacturer, product, and user-market. Employees play a vital role in achieving these objectives. Obviously, employees need to be aware of the details of the quality system and how to meet them. The Quality System (QS) regulation supports these goals by requiring that a manufacturer have sufficient qualified personnel and by requiring quality awareness training for personnel [820.25(a)]. Management with executive responsibility shall ensure their quality policy is understood, implemented, and maintained at all levels of the organization. This should be accomplished by supplying sufficient resources, training, responsibility, and authority to all managing personnel that will enable them to perform their tasks.

Personnel involved in design, manufacturing, quality assurance, auditing, complaint processing, servicing, etc., should be properly trained, both by education and experience. No matter how effective quality assurance and production systems are as concepts, people still play the major role in designing and producing a quality product. Lack of training -- as reflected in instances of negligence, poor operating techniques, or the inability of employees to discharge their functions properly -- can lead to defective products and, sometimes, to regulatory or liability problems.

Employee attitude is the most important personnel factor that can assure an effective quality system. By management setting an excellent example and through effective training, quality consciousness should be developed in every employee. Each person should be made aware of the importance of his or her individual contributions in the overall effort to achieve an acceptable level of quality.

The role of management in this vital awareness effort cannot be passive -- management should be diligent in looking for factors that indicate a need for employee training [820.25(b)]. A quality system should include an ongoing formal program for training all personnel. All personnel should be made aware that product quality is not solely the responsibility of management or any other single group. Quality is the responsibility of every employee -- any employee can generate a quality problem through ignorance of their job requirements or negligence.

FDA Observations

It is not unusual for FDA investigators to conduct factory inspections and observe employees who are clearly unaware of situations that can result in poor device quality. These employees obviously have not been properly instructed on what activities or conditions will directly cause defective devices or that can lead to mixups, contamination, or other problems that can cause non-conforming devices. For example, an improperly maintained piece of manufacturing equipment may eventually have disastrous consequences on finished devices. Therefore, the employee charged with maintaining the equipment, as well as the operator of the equipment, should be made aware of conditions that reflect a need for maintenance.

FDA investigators have observed employees: smoking near or sweeping dust into open processing tanks where the smoke and dust would destroy the usefulness of the device; blowing smoke or sweeping dust onto devices to be sterilized; handling delicate devices while wearing rings or other jewelry; wearing gloves with holes or rubbing their nose and continuing to handle devices that need to comply with bioburden requirements; wearing cleanroom clothing into uncontrolled areas; and other poor practices such as leaving windows or doors open in controlled environmental areas.

FDA investigators were advised by management that it is the manufacturer's policy not to allow the above situations to occur. The implementation of this policy is questionable. Are these employees originally and then periodically reminded of the reason: for not smoking, eating, and wearing rings; and for personal cleanliness, and other employee requirements? People respond better when they know why they are allowed or not allowed to do certain activities - not just being told that it is company policy.

GMP REQUIREMENTS

The QS regulation requires in section 820.25 that each manufacturer shall have sufficient personnel with the necessary education, background, training, and experience to assure that all activities required by this part are correctly performed. [The requirement for sufficient trained personnel is also covered by resource requirements in 820.20(b)(2) as follows. Each manufacturer shall provide adequate resources, including the assignment of trained personnel, for management, performance of work, and assessment activities, including internal quality audits, to meet the requirements of this part.]

Each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities. Training shall be documented.

As part of their training, personnel shall be made aware of device defects which may occur from the improper performance of their specific jobs. [In addition to training, personnel also have to be

notified if they are responsible for nonconforming product. The intent is to prevent or reduce nonconforming product. Each manufacturer shall establish and maintain procedures to control product that does not conform to specified requirements [820.90(a)]. The procedures shall address the identification, documentation, evaluation, segregation, and disposition of nonconforming product. The evaluation of nonconformance shall include a determination of the need for an investigation and notification of the persons or organizations responsible for the nonconformance. The evaluation and any investigation shall be documented.]

Personnel who perform verification and validation shall be made aware of defects and errors that may be encountered as part of their job functions. There are also personnel requirements in 820.70(d) and 820.75(b)(1) as follows. Each manufacturer shall establish and maintain requirements for the health, cleanliness, personal practices, and clothing of personnel if contact between such personnel and product or environment could reasonably be expected to have an adverse effect on product quality. The manufacturers shall ensure that maintenance and other personnel who are required to work temporarily under special environmental conditions are appropriately trained or supervised by a trained individual.

Each manufacturer shall ensure that validated processes are performed by qualified individual(s) [870.75(b)(1)].

Employee Selection

As the first step in meeting GMP personnel requirements, manufacturers should select or hire appropriate employees for the tasks to be performed. The initial selection of employees for a specific job is made based on a combination of education, experience, personal habits, interests, etc. For example, education alone is not a good indicator of whether a recent graduate with a scientific degree can design a product.

New employees should be informed that they are working in a regulated industry and should be initially trained to perform their specific jobs and be made aware of any defects or problems that may occur from:

- **improper performance of their assigned tasks;**
- **using incorrect tools or incorrect use of a tool;**
- **poor hygiene, poor health, or smoking or eating on the job;**
- **poor work habits or being in the wrong location; and**
- **other detrimental factors.**

Production Personnel

Section 820.70(d) requires that personnel in contact with a device or its environment shall be clean, healthy, and suitably attired where lack of cleanliness, good health, or suitable attire could adversely affect the device. Personnel who, by medical examination or supervisory observation, appear to have a condition which could adversely affect the device should be excluded from affected operations until the adverse condition is corrected. Personnel should be instructed to report such conditions to their supervisor. Such actions by management could create problems unless employees are instructed about work practices and requirements when they are hired or initially assigned to the task in an environmentally controlled area.

If eating, drinking, or smoking could have an adverse affect on the devices' fitness for use, then employees should be informed that these activities are to be done only in designated areas.

Employees need to be informed why certain personnel and work practices are required. Basic instructions about invisible microorganisms and particulates will make the company requirements much more meaningful. People respond better when they know why they are allowed or not allowed to do certain activities rather than just being told it is company policy.

Some factors that should be considered when teaching employees about working in a controlled environment include:

- **proper attire and dressing anteroom;**
- **controlled use of, and entry into, controlled areas;**
- **minimizing body movements;**
- **locating the body and hands with respect to product and airflow;**
- **prohibiting eating, drinking, smoking, or gum chewing;**
- **reducing of coughing, sneezing and other objectionable health related conditions;**
- **preventing use of lead pencils and certain cosmetics;**
- **bathing and hand washing requirements;**
- **preventing or controlling the cutting, tearing or storage of cardboard, paper, debris, etc.;**
- **eliminating electrostatic charges by selection of clothing, grounding, etc.;**
- **ensuring cleanliness of raw materials, components and tools; etc.**
- **using correct furniture and eliminating use of extra furniture;**
- **regulating the storage of tools, glassware and containers;**
- **cleaning the room and production equipment per written procedure; and**
- **cleaning of work surfaces and chairs.**

Technical Personnel

The manufacturer should assure that they have sufficient properly trained personnel, or programs to train technical personnel, to design, validate, develop processes, and produce the new or modified device. Scientific and technical personnel usually need training in:

- **regulatory requirements;**
- **company documentation systems;**
- **verification and validation techniques;**
- **consensus standards;**
- **human factors;**
- **labeling;**
- **safety;**
- **reliability;**
- **producibility; and,**
- **other peripheral design topics.**

New design personnel may be introduced to manufacturing methods and producibility issues by being assigned to various manufacturing areas before starting their design activities. The resulting

knowledge and experience is as valuable as their technical education -- remember that the ultimate objective of a design and manufacturing operation is to produce a safe and effective device.

In another valuable training technique, manufacturing personnel are assigned to assist development personnel in verifying components, and assembling and verifying subassemblies and prototype devices.

These training techniques:

- **improve communications and technology transfer between the various departments;**
- **help meet the interface requirements in 820.30(b), Design and Development Planning;**
- **help promote concurrent engineering;**
- **help research and development personnel understand that the goal is to produce a device -- not just design a device;**
- **achieve advance training for manufacturing personnel about a forthcoming design;**
- **reduce production problems by improving the producibility of the device based on the expertise and input of the manufacturing personnel into the design of the device; and**
- **reduce production problems based on the expertise and input of the device design personnel into the design of processes and production tools, jigs, molds, in-house standards, and test methods.**

All of these are important and valuable side benefits to these simple cross-training techniques. Such training should be documented.

Process Validation

The above discussion for technical personnel *also* applies to technical employees that perform process validation. After the processes are validated, these technical personnel should use their expertise and experience to develop training methods or help train production employees on how to monitor, control, and operate validated processes. Section 820.75(b) requires a manufacturer to establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that specified requirements continue to be met. Further, 820.75(b)(1) requires that validated processes be performed by qualified individuals. Obviously, operators that are trained to operate each specific validated process are needed to meet these requirements.

During the development and validation of a process, planning for eventual maintenance can reduce or prevent confusion during emergency repairs. An emergency could lead to improper repairs, such as use of a wrong replacement part. Therefore, the installation qualification should include a review of pertinent training requirements, maintenance procedures, repair parts lists, and calibration of measuring equipment.

Quality Assurance Personnel

QA or product acceptance employees shall meet the GMP personnel requirements for manufacturing employees AND shall be made aware of defects and errors likely to be found in nonconforming components and devices. Usually, it is easier and more effective to teach all of the GMP personnel requirements to all appropriate employees.

Production or QA personnel performing quality assurance or acceptance functions should :

- **Maintain requirements for health, cleanliness, and clothing standards which will prevent an adverse effect on product quality.**

- **Adequately train and/or supervise temporary personnel working in special environmental conditions.**

The production department shall have sufficient personnel with the necessary education, background, training, and experience to assure that all production activities are correctly performed. Employees are selected and/or trained for their assigned tasks. These tasks may be janitorial, receiving, pulling parts, production, labeling, acceptance test and inspection, packaging, painting, welding, mixing, specific technical tests, etc.

To meet this requirement, each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities.

As part of their training, personnel shall be made aware of device defects which may occur from the improper performance of their specific jobs. Employees should be informed that they may need to be qualified or certified to perform certain tasks such as welding, operating a validated process or working in controlled areas. Likewise, employees need to be told that where necessary, they will be informed about improper performance of their assign tasks with the intent of improving their performance and reducing the likelihood of producing nonconforming product. Where necessary, employees should be certified to perform manufacturing or quality acceptance procedures where a high degree of specialized skill is required. Training shall be documented.

Complaint Handling

It is a good idea for most of the company personnel to receive basic training in complaint handling techniques. Appropriate employees such as receptionists, salespersons, representatives, secretaries, service personnel, and other employees who talk with users should receive training on their responsibilities in regard to complaint handling requirements in section 820.198. If these employees receive a device complaint, they need to know they have a responsibility to report it to the company person(s) assigned to handle complaints. Likewise, importers and distributors should be made aware of the complaint requirements, and they should be requested to forward complaints to the manufacturer.

Management

Proper job performance by employees as required by the QS regulation dictates that management have a good knowledge of the QS regulation and resulting quality system. Therefore, management should also have appropriate education, training, and experience. As part of their

review of the quality system, management should make certain that adequate "how to do" documentation is available to employees. Proper job performance should be supported by correct and complete quality system and device master records. These records should be written in such a manner that the intended employees can understand and properly use them.

Management should show their commitment to training by providing a training room such as a cafeteria and training equipment such as chalkboards, flip charts, video cameras, VCRs, television monitors, slide projectors, overhead projectors, screens, workbooks, etc.

Training Methods

Training for employees may be achieved by many methods such as:

- **device regulatory and GMP seminars;**
- **individual consultations with managers, consultants, FDA personnel, etc.;**
- **on-the-job training with appropriate instructors;**
- **cross-training details between R&D and production;**
- **video tapes and movies;**
- **slide shows with an appropriate instructor;**
- **reading GMP/QA manuals and textbooks; and**
- **formal college QA courses.**

To meet GMP requirements, all training should be documented as noted above.

Training Indicators

A proactive approach to training is required by 820.25(b) where each manufacturer is required to establish procedures for identifying training needs. Thus, management should diligently look for factors that indicate a need for additional training or retraining. Some of these training indicators are:

- **verification failures due to basic problems,**
- **post-submission technical and labeling information required by ODE for 510(k) submissions,**
- **validation problems due to routine problems,**
- **excessive design transfer problems or delays,**
- **inadequate device master record,**
- **excessive device defects,**
- **excessive process equipment or line down-time,**
- **improper labeling or packaging,**
- **employee confusion,**
- **employees ignoring environmental control requirements,**
- **process or sterilization failures,**
- **incorrect ordering or shipment information,**
- **customer complaints, and**
- **excessive or basic items on a FDA list of observations.**

This information is derived from management observations, analysis of device history records, analysis of complaint records, quality assurance audits, etc.

Audits

As management performs their daily activities they are aware of the obvious aspects of personnel workmanship and work practices. However, to make sure that all aspects, obvious, hidden, or subtle, of the required quality system exist and are operating correctly, the QS regulation in 820.20(b) requires planned and periodic audits of the quality system. This audit covers:

- **noting personnel practices in areas being audited,**
- **looking for training indicators as listed above, and**
- **whether the company approach to training programs is proactive.**

The audit also includes an inspection and review of training:

- **programs and content,**
- **facilities,**
- **equipment, and**
- **records.**

A report should be made of each quality audit, including any reaudits(s) of deficient matters such as incorrect performance of work, lack of training, failure to update training, the training program not being proactive for all of the personnel that receive complaints, part of the training equipment is not functioning, on-the-job training not adequately supervised or documented, etc. Audit reports that cover training activities and personnel practices should be reviewed by management responsible for these factors in their department. Corrective actions for deficient training and personnel practices shall be taken where necessary (820.22).

EXHIBITS

Reprinted on the following pages is an example of an employee general training procedure and an example of associated employee training record. These may be used to comply with the training requirements of the QS regulation.

The Buildings and Environment Chapter 6 has a procedure with many details about employee practices in clean rooms.

Employee Training Procedure

This procedure is an example of a general employee training procedure that may be used by manufacturers to assure that all employees receive basic training when they are hired and are qualified for the assigned tasks. The procedure is used with the following training form.

Employee Training Record

This employee training record is a basic form for noting training activities for each employee. A few training requirements are preprinted on the form because new hires should immediately receive this basic training. The training record is used with a general training procedure as described above.

***** SAMPLE PROCEDURE *****

C O M P A N Y L O G O **Page 1 of 2**

Title Employee Training **SOP Number** _____

Prepared by _____ **Date Prepared** _____

Approved by _____ **Date** _____ **Rev** _____

ECN Notes _____

_____

Policy - Employees shall be trained as needed to perform their assigned tasks and shall be made aware that we produce medical devices in accordance with various regulations and standards.

Scope - This procedure applies to all employees.

Hiring - The education, background, training, and experience of prospective employees shall be considered with respect to the requirements of the job to be filled.

Responsibility - Managers are responsible for assuring that the employees assigned to them are trained or otherwise qualified for the assigned jobs. Before assigning an employee for the first time to a new job, managers shall check their training to verify that the employee has been trained or qualified for the new job.

The QA department is responsible for training facilities, equipment, and supplies.

Training - All inexperienced employees shall be trained to perform their assigned jobs. On-the-job training shall be monitored closely by a supervisor. All employees shall be made aware of design and/or production defects, visible and invisible, in the device, labeling, and packaging that may occur from the improper performance of their jobs and defects that they should look for and detect. Our cleanliness (environmental control) and safety procedures shall be explained to all employees.

Quality Assurance Employees - QA or product acceptance employees shall receive the training noted above and shall be made aware of errors and defects, visible and invisible, likely to be encountered as part of their quality assurance functions.

Customer Complaints - Receptionists, managers, representatives, salespersons, and other employees likely to receive complaints are trained in complaint handling procedures applicable to their functions.

Change Control - All employees are to be advised that they are to perform their jobs as instructed or as covered by standard operating procedures (SOP's). They are NOT allowed to change cleaning, compounding, processing, testing, packaging, labeling, or tasks covered by SOP's until the change is approved according to our change control SOP.

Documentation - All classroom and on-the-job training shall be documented by the supervisor and trainer of the employee on the form as shown on sheet 2. A separate form for each employee with a record of their training shall be filed and shall be updated at the end of each training session.
***** SAMPLE RECORD *****

EMPLOYEE TRAINING RECORD				Page 2 of 2
Employee Name			**Hire Date**	
DATE	**EMPLOYEE SIGNATURE**	**PRESENT JOB**	**TYPE OF TRAINING**	**SUPERVISOR / TRAINER SIGN.**
			safety	
			defect awareness	
			environment control	

6 BUILDINGS AND ENVIRONMENT

INTRODUCTION

The buildings and environment in which components, devices, and records are received, processed, built, or stored, and the personnel that perform these operations should be controlled so that finished devices will consistently meet the specifications established by the manufacturer. The degree of control should allow for appropriate changes in such elements as temperature, humidity, bioburden, particles, personnel, components, devices, and records.

PERSONNEL TRAINING

Personnel play an important role in orderly operations and environmental control. They can reduce or increase contamination. Thus, personnel can positively or negatively impact most of the points made in this chapter. To reduce problems and increase the state-of-control, employees shall be appropriately trained regarding orderly operations and environmental control as required by 820.25 and as discussed in Chapter 5.

BUILDINGS

Facilities of medical device manufacturers and their contractors in which components, in-process devices, accessories, and finished devices are handled, processed, and stored shall have sufficient space and be designed to allow proper cleaning, maintenance, and other necessary operations in order to meet the requirements of 21 CFR 820.70 of the Quality System (QS) regulation. Buildings should be suitably designed so that there is adequate space for manufacturing, receiving, packaging/labeling, storage, etc., to: minimize contaminants; assure orderly handling procedures; and prevent mixups. As the company grows or the product line is changed, existing facilities may

become inadequate. Thus, as part of the quality assurance program audit, existing buildings should be reviewed to determine if space and facilities are adequate in light of growth or changes in production

Repackers, Remanufacturers, Contract Sterilizers, and Relabelers

The GMP requirements for buildings extend to manufacturers that repackage and/or relabel unpackaged bulk devices, contract sterilizers, and remanufacturers that change the original condition of devices. The number of operations needed to repackage or relabel a product may be less than for actual manufacturing of a product; nevertheless, there is a need to design and arrange facilities so that repackaging and/or relabeling operations, particularly for sterile devices, can be performed in a controlled manner. Because remanufacturing of devices is manufacturing, the GMP requirements for buildings and facilities extend to areas where modifications are performed. In some manufacturers these modifications are done in cluttered repair shops. Under these conditions, there is an increased probability for contamination or mixup, hence such manufacturers should take appropriate precautions as required by the QS regulation.

Contamination Control

Typical problems in manufacturing and storage facilities include environmental contamination and insufficient space for receiving and holding incoming products before testing and inspection [820.70(c) and 820.70(e) and 820.70(f)]. For each area in the building where products are processed, any elements such as particulates from cardboard dust, by-products from slitting or cutting operations, microorganisms, humidity, temperature, static electricity, etc., which a manufacturer has determined might cause contamination should be controlled. Buildings should be appropriately constructed to prevent, reduce, and control potential contaminants and support the environmental control program as discussed later. For example, the control of dust may require that driveways and parking lots be paved. Crowding causes mixups and can result in contamination or in the use of unapproved or rejected products. Designated areas should be assigned for various production activities such as receiving, inspection/testing, manufacturing, labeling, packaging, record keeping, etc. Traffic by personnel who do not work in or manage the designated areas should be held to a minimum.

Orderly Operations

In addition to having sufficient space, the facility shall be designed and arranged so that all operations can be performed in an orderly manner [820.70(f)]. This will facilitate the satisfactory performance of all operations. In manufacturing areas, it prevents confusion that can lead to unsatisfactory job performance and mixups. The goal is for a smooth flow of operations.

To preclude mixups, distinct operations or processes should be separated either physically, by walls or partitions, or spatially, by providing enough room between operations to indicate that separate activities are being performed. An appropriate degree of separation, or walls, curtains, etc., should exist so that no activity will spray, dust, or otherwise have an adverse effect on other adjacent activities. For example, there should be a handling and storage system to preclude the mixup of labeled "sterile" but not-yet-sterilized devices from the same type of devices that have been sterilized. Manufacturers that have more than one labeling operation should maintain adequate separation of these to prevent any mixups occurring between various products and their specified

labeling. Labeling mixups are a major cause of product recalls and a number of these mixups can be traced to inadequate separation of operations during the labeling of devices.

ENVIRONMENTAL CONTROL

One of the variables that can significantly affect product quality and employee performance is the environment. A controlled environment is, to various degrees, an integral part of most production facilities. Some environmental factors to be considered are lighting, ventilation, temperature, humidity, pressure, particulates, and static electricity. Section 820.70(c), Environmental Control, of the QS regulation, is considered by FDA to be a "discretionary" requirement; that is, the degree of environmental control to be maintained should be consistent with the intended use of the device and details of how to achieve this control are left to the manufacturer to decide. "Discretionary quality system requirements" are those which may or may not apply to the manufacturer of a specific device. In these cases the manufacturer should decide whether implementing such requirements is necessary to assure the quality of the finished device. These requirements are modified in the QS regulation by phrases such as "where environmental conditions could reasonably be expected to have an adverse affect" and "adequately control."

General Controls

General air conditioning is normally not regarded as an environmental control; however, changes in temperature and lighting can have an adverse effect on employee performance and, in turn, on assuring that the device is properly assembled, inspected, and tested. Air conditioning can control humidity which, in turn, can affect the generation of static charges. Static charges can damage some electronic components and, in such situations, need to be controlled [820.70(c)]. Production workers are a major source of particulate contamination and standard operating procedures for personnel are often necessary in order that employees not adversely affect the environment.

Analyze Operation

If the environment in which devices are manufactured or held can have an adverse effect on the devices' fitness for use, that environment shall be controlled [820.70(c)]. For each operation, the manufacturer should analyze the manufacturing operations to identify controls needed for the finished device to meet the device specifications and be fit for the intended use; and to control costs. For example, in the manufacture of sterile devices such as implants, or diagnostic media that requires aseptic filling, the environment should be controlled to reduce viable microorganisms and particulate matter. The packaging for sterile devices should be stored in a clean, dry, insect-free area. Components that support bacterial growth should be stored in a controlled environment which, in some cases, will include refrigeration.

Because particles can bridge across sub-micron circuits and static electricity can rupture semiconductor junctions, microcircuits for use in devices should be manufactured in a stringent clean-room environment where particulates and humidity are controlled. When analyzing the production of a device to determine the degree of control needed, the manufacturer should identify exactly what needs to be controlled:

- **the device itself;**
- **the area for one task; or**
- **the large production area.**

For example, if the device can be cleaned after production, there usually is no need for extensive environmental control during production. If the cleaned devices are stored in clean containers or are immediately packaged, the environment usually should be controlled where the device is being packaged. If the work area needs to be controlled, how much should be controlled -- a work bench, room, or factory? For example, a HEPA filtered laminar-flow bench maintains a low-particulate environment that is large enough for many small tasks or operations. If a larger area is needed, then it may be possible to set a broad environmental specification for most of the room or area. A small laminar-flow unit and curtains can create a small, but very clean area. Considerations such as these can reduce environmental facility and equipment costs and reduce the activities required to maintain and monitor the controlled area and operations.

Specifications

When it is necessary to control the environment, specifications for parameters such as temperature, humidity, colony forming units (CFU's), and particulates per cubic foot, etc. should be established. No FDA guidances for these parameters presently exist for environmentally controlled areas such as clean rooms. "Federal Standard Airborne Particulate Cleanliness Classes In Clean room and Clean Zones" (FED-STD-209E) with its appendices is suggested as a resource for developing clean room standards such as particle counts per cubic foot. Federal Standard 209E defines various levels of environmental control such as Class 1000. A Class 1000 room contains no more than 1000 particles 0.5 micron diameter or larger per cubic foot of air. Information may also be obtained from manufacturers of clean room equipment. Aseptic manufacturing and filling are usually done in a Class 100 or better clean room or bench. The Class 100 status is maintained during routine operations. During idle periods the particle count will generally be much lower than 100. Some manufacturers use a Class 10,000 clean room for the assembly and packaging of devices that will be terminally sterilized and where a low particulate count on the devices is desired. The specifications for such a room could be:

Particulates:	**Maximum of 10,000 of 0.5 micron diameter or larger per cubic foot**
Humidity:	**45 +/- 5 percent**
Temperature:	**72 +/- 2.5 degrees F**
Air Velocity:	**90 feet/minute +/- 2 percent**
Air Pressure:	**0.05 inches water between the clean room and other areas**

For assembly of many types of convenience kits and assembly of medical devices that need to be free of visible particles, many manufacturers use an "industrially clean area or controlled environment area." Such rooms are air conditioned and use furnace filters and, in some cases, pre-filters of much finer porosity than furnace filters are also used. The temperature is controlled by a standard room thermostat. Humidity variations are limited by common air conditioning. True air conditioning with cooling below the dewpoint and reheat are not necessarily used. Air velocity is determined for the air conditioning; and the room is known to have positive pressure with respect to other areas by a flow or pressure indicator. A particle class is not specified. However, these manufacturers have established a controlled environment and appropriate specifications for temperature, cleaning, and contamination controls are in place. For example, filters should be replaced per schedule or as needed based on scheduled inspections. Any practices or factors from the following list that the manufacturer has deemed appropriate and elected to use should be specified and routinely performed or followed. Some additional factors that should be considered when planning and using a controlled environment include:

- **proper attire and dressing anteroom;**
- **controlled use of, and entry into, controlled areas;**
- **prohibiting eating, drinking, smoking, or gum chewing;**
- **preventing use of lead pencils;**
- **regulating the storage of glassware and containers;**
- **preventing or controlling the cutting, tearing or storage of cardboard, debris, etc.;**
- **cleaning the room and production equipment per written procedure;**
- **the original design and cleaning of work surfaces and chairs;**
- **selecting correct furniture and eliminating all nonessential equipment;**
- **controlling room air quality (amount of particulates, pressure, velocity, and exchange rate);**
- **eliminating electrostatic charges by controlling work surface composition or grounding;**
- **ensuring cleanliness of raw materials, components and tools;**
- **controlling the purity, sterility, and non-pyrogenicity of process water; and**
- **maintaining prefilters, HEPA filters, and electrostatic precipitators.**

Also see at the end of this chapter the procedure, "Clean Room and Work Station Procedure," which covers work practices, dress codes, and hygiene for employees working in clean rooms or at laminar-flow benches.

Monitoring

An appropriate system for regular monitoring should be established and maintained for each of these factors to be controlled for a given operation. This will ensure that equipment is performing properly and that the quality of the environment is within specifications. When a particle count Class is specified, monitoring of airborne particulates is usually done with an air sampler. Monitoring of work surfaces for microbes [colony forming units] may be done with surface contact plates or settling plates. However, settling plates should not be used for monitoring when horizontal laminar air flow is used as they are ineffective for this type of flow.

All sampling should be done per written procedure, and the data should be recorded. Further, periodic inspections of environmental controls and documentation of the inspections are required by the QS regulation. The inspection checkoff form or other record should be kept simple.

CONTAMINATION CONTROL

The QS regulation requires in 820.70(e) that every manufacturer establish and maintain procedures to prevent contamination of product or equipment. These process specifications are established by the manufacturer to ensure that finished devices will meet the company's quality claims. Typical device examples are: in vitro devices that are not contaminated with microbes, detergents or rodenticides; circuits that are not contaminated with flux; implants that are not contaminated with body oils and certain implants that are not contaminated with pyrogens. Pyrogens are substances that cause fever in humans, and they arise primarily from cellular debris of gram-negative bacteria.Certain implants such as orthopedic implants are not required or expected to be pyrogen free. Other devices are required to be nonpyrogenic including: transfusion and infusion assemblies, devices that come in contact with circulating blood or cerebrospinal fluid, intraocular lenses and the surgical instruments used in their implantation, and any device labeled as "nonpyrogenic". Manufacturers should carefully control the environment in which such devices are

manufactured and processed to minimize contamination with bacteria or establish a procedure for cleaning the devices.

If necessary for the device to meet company product specifications or labeling claims, cleaning procedures and schedules to meet the requirements of section 820.70 may need to be written. Each operation should be analyzed in order to write an appropriate procedure or determine that one is not needed. For example, written procedures are usually not required for cleaning floors and work benches in areas where non-sterile and non-growth promoting components or devices are processed and packaged. An example of a procedure and schedule for cleaning an aseptic filling room is exhibited at the end of this chapter. Records related to facilities, the environment and personnel practices need to be kept simple as shown by this example. Note that the schedule and record of cleaning are both on page 4 of the procedure. The record of cleaning may be a checkmark, initial, or signature. Where a checkmark is used for repetitive work, companies commonly require that the person's name be on the record at least once. The schedule for cleaning may be posted or filed as long as it is in a convenient location. As appropriate, manufacturers may use this procedure as is, modify it, or use it as a guide to develop a procedure to meet specific needs.

Personnel Sanitation Practices

Adequate bathroom, dressing, storage, and waste facilities should be provided, as appropriate, for personnel to maintain the needed level of cleanliness [820.70(d)]. Such facilities should be maintained on a regularly scheduled basis. Where necessary, such as in a clean room, special clothing and an area to don and store the garments should be provided. Clean room clothing is not be worn into uncontrolled rooms or outside the facility.

Prevent Contamination by Hazardous Substances

If rodenticides, insecticides, or other hazardous substances are used, written procedures to limit their use or for their removal from work surfaces and devices should be established to prevent any adverse affect on the manufacturing process or the device [820.70(e)].

Personal Practices

If eating, drinking, or smoking could have an adverse affect on the devices' fitness for use, manufacturing procedures should include instructions on how to avoid such adverse effects [820.70(d)]. For example, these activities could be confined to specially designated areas such as a lunch room or employees lounge. Directions and containers or equipment should be provided for timely and safe disposal of trash, by-products, effluents and other refuse.

EXHIBITS

Reprinted on the following pages are two examples of procedures that may be used to comply with the cleaning or contamination control requirements of the QS regulation. Both of these procedures deal with sensitive areas of the plant: clean room and aseptic filling rooms. Therefore, these are more comprehensive than is normally needed for general plant cleaning.

Note that these procedures follow good labeling practices in that the tasks or rules are broken into numbered steps; and only one or two activities or rules are included in each step. Thus, the directions or rules are easy to read, remember, and execute or obey.

Clean Room and Work Station Procedure

This procedure is divided into general requirements, non-laminar airflow clean rooms, and workstations, laminar airflow clean rooms and workstations, and clean room personnel rules. The first part of this procedure contains useful information for any area of a plant were moderate control is needed to reduce particulate contamination. The level of control needed increases as the procedure goes from non-laminar airflow to laminar airflow. The final section contains additional requirements for personnel working in a clean room.

Cleaning Procedure for the Aseptic Filling Room

This is a standard operating procedure used by personnel that are charged with cleaning an aseptic filling area and not for personnel that generally work in this area. This cleaning procedure is divided into two sections, daily and weekly tasks, thus giving personnel guidance on when, as well as, how to perform these tasks. Please note that many manufacturers will alternate the germicide in their cleaning solution to minimize the likelihood of resistant organisms developing. There are two items of interest in this procedure that should help to minimize entering and exiting this area: the equipment list at the beginning, and the maintenance information at the end. The equipment list is important because it alerts personnel to obtain the proper equipment before beginning work. The maintenance procedures allow the personnel to perform maintenance tasks without calling in a special crew or having to exit and re-enter the room unnecessarily.

PROCEDURE TITLE: Clean Room and Work Station Procedure No._____ Rev._____

Prepared by_____App. by_____Date_____

A. General Requirements

1. No eating, drinking, smoking, or chewing gum.

2. Specified garments must be worn when entering and inside the clean area. These shall be stored in the anteroom and not worn in non-clean areas.

3. Only approved clean room paper shall be allowed in the area.

4. Use only ballpoint pens (fine point preferred).

5. Rouge, lipstick, eye shadow, eyebrow pencil, mascara, and false eyelashes shall not be worn by any worker while in any clean area.

6. **No cosmetics of any kind are to be applied or removed in the clean area.**

7. **Skin lotions or lanolin-base soaps are in the restrooms for employees to use to guard against flaking due to dry skin.**

8. **Solvent contact with the bare skin should be avoided, as most solvents will remove the natural skin oils and cause excessive skin flaking.**

9. **The use of paper or fabric towels is not recommended -- washrooms should have electrically powered, warm-air dryers.**

10. **Approved pliers, tweezers or lint-free gloves must be used to handle manufacturing materials, components, or finished devices.**

11. **Do not touch with gloves or finger cots any covered or uncovered part of the body, or any item or surface that has not been thoroughly cleaned.**

12. **All containers, racks, jigs, fixtures, and tools should be cleaned to the same level of cleanliness specified for the device being processed.**

B. Non-laminar Airflow Clean rooms and Work Stations

1. Garments shall be pocket-less, lint-free coveralls, with snug fitting fasteners at the neck, wrist, and ankles.

2. Lint-free caps must be worn and must completely cover the hair and head except for the eyes, nose, mouth, and chin.

3. Shoes shall be cleaned and covered with a non-shedding boot-type cover or changed to approved clean room footwear. If special footwear is provided, it shall not be worn outside the clean room and dressing room.

4. Janitorial services shall be performed only by adequately trained and supervised personnel, each of whom must be properly garbed.

5. All equipment to be brought into the clean room shall be qualified for clean room use and first be thoroughly cleaned. Use only equipment that will minimize the generation of contaminants.

6. Traffic into and within the clean room shall be restricted to authorized and properly garbed personnel, and unnecessary movements by these personnel shall be minimized.

C. Laminar Airflow Clean Rooms and Work Stations

1. Garments may vary with the operation being performed, but the minimum garment shall be a pocket-less, lint-free smock which extends to at least 15 inches below the work surface. The collar and cuffs shall have fasteners.

2. Head covering shall be worn, and shall completely cover the hair. If the operation requires the wearer to lean over the work, or move into the airstream between the filter bank and the work piece, the front, sides, and rear neck areas of the head shall also be covered.

3. Shoe covers are not necessary for vertical or horizontal laminar airflow facilities except when the work is being performed less than 24 inches from the floor.

4. A face mask may be needed if an operator has a cold, or if the nose and mouth must be brought very close to the work piece for work on miniature components or devices. Check with your supervisor for instructions.

D. Clean Room Personnel Rules

Personnel will be asked to cooperate in maintaining a low contaminant emission rate by observing the following rules.

1. **Bathe at night, instead of in the morning, to allow the build-up of normal body oils which reduces skni shedding. Also, use skin lotions.**

2. **Wear clean, unstarched, low-shedding garments.**

3. **Where appropriate, shave daily and be clean shaven or wear appropriate hair covering.**

4. **Avoid touching, rubbing, and scratching exposed areas of the body.**

5. **Exercise extra care to rid the hands of normal residue from home duties such as starching, baking, plastering, wallpapering, painting, concrete work, carpentering or other particulate generating activity.**

6. **Request duty outside the or away from the clean room area when you have a cold or other viral or bacterial infection.**

STANDARD OPERATING PROCEDURE: Number G021 Revision A

TITLE: Cleaning Procedure for the Aseptic Filling Room

APPROVED BY:_____Date:_____

PURPOSE: Control of surface contamination within the Aseptic Filling Room.

EQUIPMENT NEEDED:

1. **Cleaning solution: See SOP G044**
2. **Non-linting wiping cloths**
3. **Stainless-steel basins and pails**
4. **Dry-wet vacuum cleaner for floors (should be equipped with a HEPA filter on the exhaust air port to filter the exhaust air)**
5. **Sponge mops with replaceable sterile heads**
6. **Mop buckets**
7. **Stainless-steel sponges**
8. **Powder free latex surgical gloves, sterile**
9. **Head and shoe covers, sterile**
10. **Face masks and gowns, sterile**
11. **Stainless-steel cart**
12. **Sprayer**
13. **Trash can plastic liners**
14. **Stepladder**

DAILY CLEANING REQUIREMENTS:

CAUTION: Be careful when using stepladder and when walking in wet areas. USE EXTREME CARE WHEN CLEANING ELECTRICAL FIXTURES AND OUTLETS. USE DAMP (NOT WET) CLOTH TO WIPE ELECTRICAL ITEMS.

A. Gowning Room:

Shoe and head covers are required in this area. Begin all cleaning at the top and finish at the bottom of any equipment or surface to be cleaned.

1. **Empty trash containers and replace plastic liners.**
2. **Replenish stock of shoe covers, masks, head covers, gowns, gloves and put into proper areas.**
3. **Fill dispenser with 0.45 u filtered 70% Isopropyl alcohol.**
4. **Mix cleaning solution of XXXXXXXX using process water (SOP G044).**

5. **Fill a stainless-steel basin with cleaning solution and begin wiping in this order: the boot box; stool; wash station; top and outsides of all cabinets; counter tops; and the tops of the trash containers.**
6. **Remove excess debris and wet mop the floor with cleaning solution.**
7. **Fill sprayer with cleaning solution and wet the floor; allow it to air dry.**
8. **Gown according to gowning procedures and go into the filling area (SOP G014).**

B. Filling Room:

1. **Move any remaining products (devices) to appropriate areas as directed by your supervisor.**
2. **Empty all trash containers and replace liners.**
3. **Remove particulate matter from ledges, cabinets and external surfaces of laminar-flow benches with a wiping cloth and cleaning solution.**
4. **Perform general cleaning and organization of shelves.**
5. **Remove debris and wet mop the floor with cleaning solution.**
6. **Spray the entire floor in the filling room with cleaning solution, using the provided sprayer. Allow the floor to air dry.**

WEEKLY CLEANING REQUIREMENTS:

All daily cleaning requirements are included in the weekly cleaning requirements. The additions to the weekly cleaning are ceilings, walls, and the internal work surfaces of the laminar-flow work benches. Rodac™ plate measurements are taken after cleaning and before the next production shift.

A. Gowning Room:

1. **Use only one entrance and one exit when cleaning. The cleaning direction will flow from entrance to exit.**
2. **Remove all non-essential equipment from the room and clean it. Return the equipment after the entire area is cleaned.**
3. **Begin cleaning the room by wiping the entire ceiling area with the cleaning solution.**

Frequent changes of the cleaning solution and the wiping cloths are needed for effective cleaning of large areas such as the ceilings and walls. Make new solution and change wiping cloths when dirty.

1. **Clean air vents, lighting fixtures, and sprinkler heads.**

1. **Clean the walls next, starting at the top and cleaning toward the floor.**
2. **When the ceilings and walls are cleaned, follow steps 1, 2, 3 and 5 of the Daily Cleaning Requirements for the gowning room.**
3. **Remove debris and wet mop the floor with cleaning solution.**
4. **Fill the sprayer with cleaning solution and wet the floor. Allow to air dry.**
5. **Gown according to procedure and go into the Filling room (SOP G014).**

B. Filling Room:

1. **Follow steps 1, 2, 3 and 4 of Daily Cleaning Requirements for Filling Room.**
2. **Begin cleaning operation by wiping the entire ceiling area with cleaning solution. Make new cleaning solution and change wiping cloth when visibly dirty.**
3. **Clean air vents, ultraviolet and fluorescent lighting fixtures and sprinkler heads.**
4. **Clean the ultraviolet bulb since any oil or dust on the bulb drastically reduces its germicidal properties.**
5. **Clean the walls next, starting at the top and cleaning toward the floor. Make new cleaning solution, and change wiping cloth when dirty.**
6. **Empty all shelves and wipe with the cleaning solution. Wipe the removed materials and put them back onto the cleaned shelf.**
7. **Wipe all cabinets and equipment with the cleaning solution from top to bottom.**
8. **Wipe all ledges and surfaces with the cleaning solution.**
9. **Pay particular attention to the laminar-flow workbenches because the cleaning operation should start in the internal work surface of the hood as it is the cleanest area.**

Use a fresh wiping cloth and cleaning solution for the internal work surfaces. Do not use the same cloth or solution which was used for the external cleaning. Discard solution and wiping cloths after cleaning each hood.

1. **First, switch off the laminar-flow hood, then clean all outside surfaces from top of hood to bottom stand. Discard cleaning cloth.**
2. **Second, clean all internal work surfaces with a new cleaning cloth in this order:**

    a. **Air diffuser screen**
    b. **Workbench top.**
    c. **Plexiglas sides**
    d. **Light covers**

3. **Clean the floors. Scrub stains or spills first, with stainless-steel sponges, to loosen debris. Use the sponge mop to clean the loosened debris. Fill the sprayer with cleaning solution and wet the entire floor area. Allow to air dry. Rodac™ plate measurements are made after cleaning and before the next production shift.**
4. **Complete the documentation ledger and sign it. See Attachment A.**

C. Maintenance of Cleaning Equipment After Daily and Weekly Cleaning:

1. Use the same solution as used for general cleaning.
2. Wipe stepladder from top to bottom, in that order, and put it into storage cabinet.
3. Wipe stainless-steel basins and pails with cleaning solution, allow to air dry, and put into storage cabinet.
4. Rinse mops and buckets with cleaning solution. Do not leave dirty solution in buckets or vacuum cleaner.
5. Rinse sponge mops with warm water. If mop head needs replacing, replace it and put mop into storage cabinet.
6. Wipe stainless-steel cart with cleaning solution and put into storage cabinet.
7. Rinse sprayer with cleaning solution and put into storage cabinet.
8. Rinse vacuum cleaner with cleaning solution. Remove filters and clean with cleaning solution. Replace filters and clean nozzle. Put into storage cabinet.
9. Autoclave mop heads and buckets per procedure GAC 09.

PTIC FILL DEPARTMENT CLEANING RECORD Week of									
A	ITEM	SUN	MON	TUE	WED	THU	FRI	SAT	WKLY
NING ROOM	Empty waste containers								
	Remove dirty uniforms								
	Wipe ceilings								
	Clean UV lights								
	Wipe walls								
	Clean floors								
ROOM	Empty waste containers								
	Straighten shelves								
	Wipe ceilings, walls & ledges								
	Clean UV lights								
	Clean floors								
LOCKS	Wipe ceiling & walls								
	Clean floors								
AN FILL RM	Empty waste containers								
	Wipe ceilings & walls								
	Clean floors								
LING AREA	Empty waste containers								
	Wipe ceilings, walls & ledges								
	Clean UV lights								
	Clean floors								

e task completed each day by a check mark in appropriate box. Shift Supervisor: _____

7 EQUIPMENT AND CALIBRATION

INTRODUCTION

The Quality System (QS) regulation requires that each manufacturer develop, conduct, control, and monitor production processes to ensure that the end device conforms to its specifications [820.70]. All equipment used to manufacture a device shall be appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use [820.70(g)]. The degree of maintenance on equipment and the frequency of calibration of measuring equipment will depend upon the type of equipment, frequency of use, and importance in the manufacturing process. Where deviations from device specifications could occur as the result of manufacturing processes, the manufacturer shall establish and maintain process control procedures. This chapter addresses the

steps necessary to ensure that manufacturing equipment continuously operates within the parameters necessary to produce a product that meets specifications.

EQUIPMENT GMP CONTROLS

The selection, purchase, and installation of the most appropriate manufacturing equipment is important to successfully manufacture a medical device to specifications. After this manufacturing equipment has been installed and placed in operation, it shall be maintained. This includes the periodic inspection, adjustment, cleaning, and other maintenance of this equipment to insure that product specifications continue to be met [820.70(g)(1), (2) and (3)]. If the manufacturing equipment used in production includes computers or an automated data processing system, the manufacturer shall validate the software for its intended use and the software changes using an established protocol [820.70(i)]. In addition the manufacturer is responsible for ensuring the establishment of routine calibration [820.72], inspection, and maintenance on all of their inspection, measuring, and test equipment so this equipment will be suitable for its intended use(s).

Equally important to the purchasing and maintenance of manufacturing equipment is the adequate training of personnel so they are able to operate the equipment correctly [820.25(b) and 820.70(d)]. This training shall be documented. Included in adequate personnel training is the establishment and maintenance of requirements for health, cleanliness, personal practices, and clothing of employees when contact between these people and the product or the environment could reasonably be expected to adversely effect the finished product quality [820.70(d)].

Maintenance

Device manufacturers shall establish schedules to maintain, clean, and adjust equipment used in the manufacture of medical devices where failure to do so could have an adverse effect on the equipment's operation and hence the device. For example, failure to maintain, clean, and adjust a sealing and/or packaging machine used for primary packaging of sterile devices will eventually result in defective packages and thus nonsterile products.

A manufacturer should determine if the equipment requires maintenance and apply the appropriate parts of the GMP requirements for equipment. The user usually can determine if specific equipment requires maintenance by reviewing the equipment operations and maintenance manuals usually supplied by the equipment manufacturer. Typically, a manufacturer will maintain equipment simply because it prolongs equipment life and minimizes the need for major service.

If it is necessary to maintain, clean, or adjust equipment, the manufacturer should:

- **have a written schedule for performing these activities;**
- **where adjustment is necessary to maintain proper operation, post the inherent limitations and allowable tolerances of the equipment or make these readily available to personnel responsible for making the adjustments;**
- **document the maintenance activities including the date and individual(s) performing the maintenance activity and the date and individual(s) conducting the inspections;**

- **have procedures for conducting periodic inspections to assure adherence to maintenance schedules; and,**

- **audit the activities and document the inspection.**

Records

Manufacturers may find it helpful to establish and maintain maintenance procedures for manufacturing equipment in order to ensure meeting the manufacturing specifications. These procedures should include adjustment and cleaning, as well as other equipment maintenance. Documentation should be kept on maintenance activities including: the activity performed, the date, and the individual providing the maintenance [820.70(g)(1)]. An example of an operation and maintenance procedure, "P.C. Board Cleaning," is exhibited at the end of this chapter. Maintenance records and schedules are not needed for equipment such as lathes, presses, grinders, etc., that are used in a machine shop and maintained by skilled employees on a daily basis. Automated machining equipment will require maintenance schedules.

MANUFACTURING MATERIALS

The proper or optimum operation of manufacturing equipment often requires the use of lubricants and other manufacturing materials. The QS regulation defines "manufacturing material" as any material or substance used in or used to facilitate the manufacturing process, a concomitant constituent, or a byproduct constituent produced during the manufacturing process, which is present in or on the finished device as a residue or impurity not by design or intent of the manufacturer [820.3(p)]. Manufacturing materials are often used with equipment. Manufacturing materials include, but are not limited to: mold release compounds; cleaning agents; lubricating oils; and other substances used to facilitate manufacturing. If any of these materials has an adverse effect on the finished device, procedures shall be established and maintained for the removal or at least the reduction of these manufacturing materials to an amount that will not adversely affect the device's quality.

Manufacturing materials are specified, procured, inspected/tested, etc., the same as components [820.3(r), 820.50, and 820.80]. For details see Purchasing and Acceptance Activities, Chapter 10 of this manual.

Analyze Use

The use of manufacturing materials that may adversely affect the finished device should be carefully analyzed. Each process should be designed to use a minimum amount of adverse materials so as to reduce costs, reduce removal efforts, and increase the intrinsic safety of the device. Whether or not a manufacturing material has been removed or adequately limited may be determined by using either of the two general approaches below.

- **The adverse material may be measured directly and compared to the process specification.**

- **If feasible, the component, in-process device, or finished device may be tested against its specification. If the item passes, it follows that the residue is not affecting the performance.**

The test specification should be appropriate for this method of evaluating residues and may need to include tests for toxicity, pyrogens, material compatibility, etc.

Control Use

Section 820.70(h) requires a written procedure for the use and removal of manufacturing materials that can have an adverse effect on devices. Usually, the procedure used for routine cleaning of the device and its assemblies can be used for this purpose. If so, a special procedure is not necessary. However, when residues from agents such as ethylene oxide should be reduced, special instructions usually are necessary.

When manufacturing materials such as oils, mold-release compounds, gases, cleaning agents, etc., are used on or in equipment, manufacturers should:

- **provide written procedures for the use and removal of materials; and**
- **remove the material or limit it to a safe amount;**
- **document the removal.**

Where a manufacturing material residue is not or cannot be made safe for everyone such as for sensitized individuals, the manufacture should meet limits set by regulation, standards, guidance, etc. When appropriate, a caution label should be used to advise sensitized or atopic individuals about the residue.

A sample procedure, "P.C. Board Cleaning", covering equipment used for removing adverse manufacturing materials (flux and debris) is exhibited at the end of this chapter. This procedure covers the removal of flux, finger oils, debris, etc., from printed circuit (PC) boards. In some cases, flux is an adverse manufacturing material.

AUTOMATED PRODUCTION AND QA SYSTEMS

The hardware system, software program, and general quality assurance system controls discussed below are essential in the automated manufacture of medical devices. The systematic validation of software and associated equipment will assure compliance with the QS regulation; and reduce confusion, increase employee morale, reduce costs, and improve quality. Further, proper validation will smooth the integration of automated production and quality assurance equipment into manufacturing operations.

Medical devices and the manufacturing processes used to produce them vary from the simple to the very complex. Thus, the QS regulation needs to be and is a flexible quality system. This flexibility is valuable as more device manufacturers move to automated production, test/inspection, and record-keeping systems.

Software Validation Guidances

The QS regulation requires in 820.70(i) that software programs be validated for their intended use according to an established protocol when computers are used as part of an automated production or a part of the quality system. Software used in automated production and quality systems consists of programs or codes that cause computerized equipment to perform desired tasks,

plus operator manuals and instructions. FDA has drafted an information document, "Application of the Medical Device GMPs to Computerized Devices and Manufacturing Processes," which is reprinted in the Appendix. Also, a document entitled, "Reviewer Guidance For Computer Controlled Medical Devices Undergoing 510(k) Review," is available from DSMA. Both of these documents can be used with the QS regulation to help establish a software QA and validation program.

There are also standards, books, and articles that can be used for guidance. Military Specification MIL-S-52779A and the Institute of Electrical and Electronic Engineers (IEEE) "Standard for Software Quality Assurance Plan" (IEEE Std 730-1984) are examples. Manufacturers, however, should not rely completely on such documents, but should examine their software needs and develop whatever controls are necessary to assure software is adequate for its intended use.

Employee Responsibility and Training

The device manufacturer should identify individuals or departments responsible for software quality and clearly specify their responsibilities. These individuals and/or department personnel should have sufficient training, authority, responsibility, and freedom of action to specify and evaluate the design and use of software and associated equipment.

A manufacturer probably will experience problems if employees operating the automated system or inputting data do not have adequate background and/or training. Employees should have adequate knowledge of the system through both formal training and on-the-job experience. Those responsible for data input should be able to recognize data errors (820.25). The QS regulation requires that processes be controlled (820.70). Thus, automated systems should be designed [820.70(a)] and employees trained (820.25) to help prevent inaccurate data input or adjustments. This requirement can be accomplished by the aforementioned training and by software controls. Where practical, software programs should have built-in error controls such as prompts, alpha-only fields, numeric only fields, length limits, range limits, and sign (+or -) control to help eliminate mistakes during data entry. These error-control or human-factors requirements, as appropriate, should be part of the specifications for software being developed or purchased.

Formal Development of Software

Manufacturers that develop their own process control software shall follow the design controls in 820.30 and document each step of the development. The software should be appropriately structured and documented so that any future changes can be accomplished, even by a different programmer, with a minimum of difficulty and maximum reliability.

To validate software, it should be:

- **structured, documented and verified as it is developed;**
- **checked to make sure that it meets specifications;**
- **adequately tested with the assigned hardware systems; and**
- **operated under varied conditions by the intended operators or persons of like training to assure that it will perform consistently and correctly.**

Each module or routine of the program should be verified to make sure it performs the specified function. The main core of the program should be checked to make certain that all parameters are correctly initialized and that data is correctly transferred between the routines. The input-output routines should be checked for proper operation with the intended peripherals to the extent feasible at this stage of the development. The testing is performed with real or simulated input data. The input data should accurately represent the real data that will occur in the next phase of testing. This input data should include data at the boundaries of acceptability, i.e., limit testing. The test protocol, data and results should be documented. The documentation should be made available to the party, who will evaluate the software with the automated production or quality assurance equipment to be used in routine manufacturing.

The testing of the software with the actual medical device production or testing equipment should exercise program functions under expected production conditions. The testing should include the input of normal and abnormal (limited case) data to test program performance and error handling. The validation should assure that the software and associated equipment meet the company specifications. The test protocol, testing, results, and design review should be documented in the design history file. Procedures for use and maintenance of the equipment and acceptance of the output product are documented in the device master record. Any serious deficiencies should be corrected.

Commercial Software and Equipment

When an outside contractor is engaged to develop software, the device manufacturer should make sure that the contractor clearly understands the software requirements and translates them into documented specifications with sufficient objectivity that compliance can be measured. FDA recognizes that most of the validation may be done by the contractor, however, the device manufacturer is still responsible for the adequacy and the validation of the software for its intended use. Therefore, the contractor should be required to develop the software according to a quality system plan that includes validation.

When possible, the purchaser also should conduct pre-award audits to verify adequacy of the contractor's quality system. Two key elements that should be checked are the contractor's test plans and system for controlling changes to documentation. Subsequent audits should be conducted as needed to verify that the contractor is complying with the quality system plan. The manufacturer who has custom software prepared and validated by a contractor should ensure the software program is running properly and producing correct results before using the program to produce medical devices for distribution.

Manufacturers who purchase commercial equipment with incorporated software should validate the software and associated equipment for the intended applications. If, however, the software has been validated by the developer and proven through use, the purchaser need not test it as comprehensively as new software. For example, automated production and test equipment that is controlled by software can usually be validated through use of a "dummy" device. This "dummy" device should exercise functions and decisions in normal and limit-case situations that may reasonably be expected during production. In some cases, suppliers provide test programs that may be used to assure that the equipment will appropriately and accurately perform all intended functions before it is used for routine production.

Validation of Automated Equipment and Processes

Validated, automated machine tools such as lathes, printed-circuit drills, and component inserters usually can be monitored and maintained by conducting a first and last-piece inspection of representative product lots. The record of this activity may be noted on the routine quality control or production records for the machine. Validation of complex microprocessor-controlled equipment, such as sterilizers or to verify satisfactory operation is generally a more extensive activity than the validation of machine tools. Typically, verification should be done by using calibrated measurement instruments to check the actual parameters achieved during trial runs, and comparing these measurements with the set points and data outputs of the automated system. In all cases, under the QS regulation the user is responsible for:

- **assuring the adequacy of automated equipment and software;**
- **verifying that all intended functions will be correctly and reliably performed; and**
- **maintaining appropriate records.**

Validation records [820.70(i)] for software and automated equipment can be maintained by the user in the design history file [820.30(j)], the device history record [820.184], or the quality system record [820.186], depending on what works best for the manufacturer. Specifications for the hardware and software including directions for their use, if any, shall be included or referenced in the device master record [820.181]. The device master record [820.3(j)], as explained in Chapter 8, is a compilation of records containing procedures and specifications for a finished device. The device master record (DMR) contains or references the records covering the use of the equipment and the specifications of the output product. Upon request, these records shall be made available to FDA investigators for review and copying during their audit [820.180] of the manufacturer's GMP system.

All changes to software programs shall be formally reviewed and approved before implementation [820.30, 820.70 and 820.40]. Because changes in one part of software can affect other parts of software, adequate consideration should be given to side-effects of these changes. Such changes are much easier to make and evaluate when the original software is appropriately structured and thoroughly documented.

Automated Data Collection and Processing

In addition to aiding the production of devices, computers may be used to collect and maintain quality control and production records. These records are called the device history record in the QS regulation. A device history record [820.3(i)] is a compilation of records containing the production history of a finished device. When design history files, device history records, device master records, or quality system records are maintained by computer, appropriate controls should be used to assure that data is entered accurately, changes are instituted only by authorized personnel, and records are secure. Hard copy or alternative systems such as backups [820.180], duplicates, tapes, or microfilm should also be used to avoid losing records as a result of inadvertent erasure or other catastrophe. As appropriate, access to records and data bases should be restricted to designated individuals.

The increased use of computers and related input/output peripherals has affected FDA policy regarding GMP signature requirements. In response to the use of electronic technology, FDA has

issued an advisory opinion stating that magnetically coded badges or other computer-compatible identifiers may be used in lieu of signatures as long as there are adequate controls to prevent inaccurate data input. If coded badges and the like are not controlled (i.e., not restricted to designated employees), they will not meet the applicable GMP requirements.

Manufacturers may wish to keep appropriate records such as device master records and complaint files at central or corporate offices. If the overall data handling system is controlled as stated above, manufacturers may maintain appropriate quality system records at central locations if they can transmit these records to the manufacturing establishment by computer plus modem, or other high speed data transfer system.

Equipment Controls and Audits

Automated equipment and any peripheral equipment requiring maintenance and/or calibration shall be included in a formal calibration and maintenance program [820.72]. Also, environmental factors such as temperature, humidity, contamination, static electricity, magnetic fields, and power-supply fluctuations can adversely affect automated equipment and data storage equipment such as magnetic discs, tapes, optical systems, etc. Consequently, necessary precautions, environmental controls, and maintenance programs [820.70] shall be implemented to prevent adverse effects on the equipment and stored data.

During the quality system audit [820.22], manufacturers shall audit the use and control of their automated production and quality systems. The audit should include software and equipment maintenance procedures and records, and should evaluate the adequacy of security measures, change controls, and other controls necessary to maintain software quality and proper performance of associated equipment. The audit shall be documented, important results reviewed with management, and corrective action taken as appropriate.

MEASURING EQUIPMENT CALIBRATION

The QS regulation is intended to help assure that devices will be safe, effective, and in compliance with the FD&C Act. To support this goal, each medical device manufacturer should develop and implement a quality system that assures, with a high degree of confidence, that all finished devices meet the company's device master record specifications. These specifications should, in turn, reflect the company quality claims. Section 501(c) of the FD&C Act states a device shall be deemed to be adulterated if its strength differs from, or its purity or quality falls below, that which it purports (claims). Such assurance is obtained by many activities including the measurement of component, device, and process parameters during design and production. These measurements shall be made with appropriate and calibrated equipment as required by 820.72.

Each manufacturer should assure that production equipment and quality assurance measurement equipment, including mechanical, electronic, automated, chemical, or other equipment, are:

- **suitable for the intended use in the design, manufacture, and testing of components, in-process devices and finished devices;**

- **capable of producing valid results;**

- **operated by trained employees; and**

- **properly calibrated versus a suitable standard.**

To succeed, the quality system shall include a calibration program that is at least as stringent as that required by the QS regulation (820.72). The intent of the GMP calibration requirements is to assure adequate and continuous performance of measurement equipment with respect to accuracy, precision, etc. The calibration program implemented by a company may be as simple or as sophisticated as required for the measurements to be made. Some instruments need only be checked to see that their performance is within specified limits, while others may require extensive calibration to a specification.

Manufacturers should determine which measurements are necessary to assure that finished devices meet approved device master record specifications, and assure these measuring instruments are included in a calibration program. Measurement equipment should be identified by label, tag, color code, etc., when located in the same areas as instruments that are not part of the calibration system. Identification can assure that proper equipment is employed to verify and determine compliance to specification of a device component, in-process device, or finished device.

Sometimes equipment used only for monitoring a parameter need not be calibrated but should be identified (e.g., for monitoring). A monitoring function might be to indicate if a voltage or other parameter exists, but the exact value is not important.

Calibration Requirements

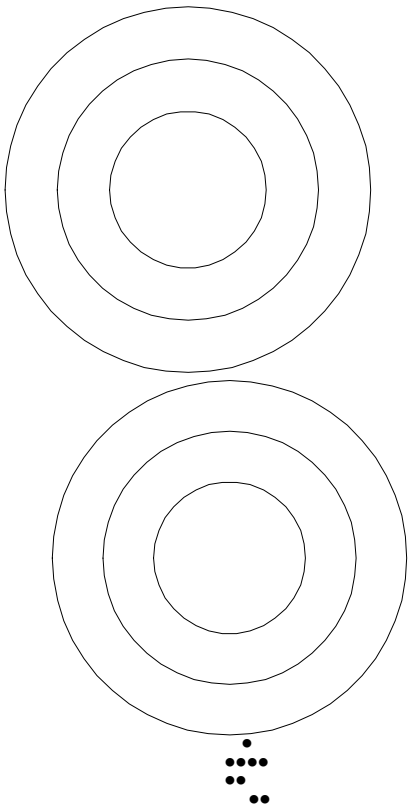
The QS regulation requires in section 820.72(b) that equipment be calibrated according to written procedures that include specific directions and limits for accuracy and precision. Figure 5.1 illustrates bias, precision, and accuracy.

Precision has no unit of measure and only indicates a relative degree of repeatability, i.e., how closely the values within a series of replicate measurements agree with each other. Repeatability is the result of resolution and stability.

Bias is a measure of how closely the mean value in a series of replicate measurements approaches the true value. The mean value is that number attained by dividing the sum of the individual values in a series by the total number of individual values.

Accuracy is the measure of an instrument's capability to approach a true or absolute value. Accuracy is a function of precision and bias. Because different manufacturers have different accuracy requirements, each manufacturer should decide the level of accuracy required for each measurement and provide equipment to achieve that accuracy.

large bias + high precision
= low accuracy



zero bias + high precision
= high accuracy

large bias + low precision
= low accuracy

zero bias + low precision
= low accuracy

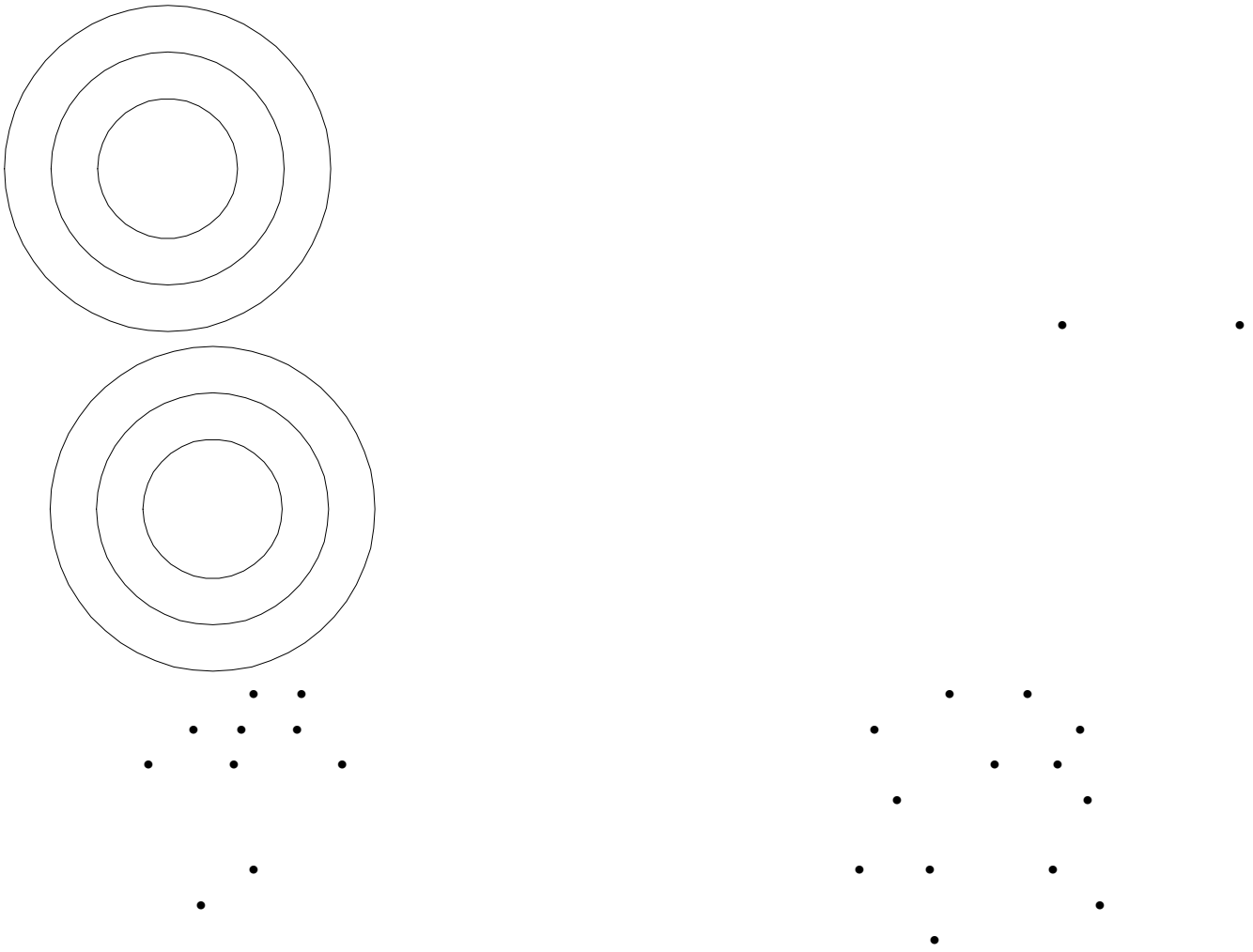


Figure 5.1 Bias, Precision and Accuracy

Proper and periodic calibration will assure that the selected equipment continues to have the desired accuracy. GMP calibration requirements are:

- **routine calibration according to written procedures;**
- **documentation of the calibration of each piece of equipment requiring calibration;**
- **specification of accuracy and precision limits;**
- **training of calibration personnel;**
- **use of standards traceable to the National Institute of Standards and Technology (NIST), other recognizable standards, or when necessary, in-house standards; and**
- **provisions for remedial action to evaluate whether there was any adverse effect on the device's quality.**

Remedial action includes recalibration and evaluation of the impact of out-of-tolerance measurements:

- **on the device design or process validation parameters or data;**
- **on the quality of existing components, in-process, or finished devices; and**
- **appropriate corrective action.**

Equipment Selection

The manufacturer should establish and maintain procedures to ensure that purchased and otherwise received equipment and associated supplies conform to specified requirements (820.50). The purchase of stable and accurate measuring equipment can reduce the frequency of calibration and increase confidence in the company's metrology program. Where economically feasible, equipment with more accuracy than needed for various measurements can be used longer without recalibration than equipment that marginally meets the desired accuracy requirements. Delicate instruments, however, that are "pushing the state-of-the-art" should not be used for routine measurements unless no other approach is feasible.

Procedures

There are a number of sources of information from which calibration procedures can be developed. Instrumentation manufacturers often include calibration instructions with their instruction manuals. Although these instructions alone are not adequate to meet the QS requirements for a calibration procedure, they usually can be used for the actual calibration process. In some cases, voluntary standards exist such as those by the American Society for Testing and Materials (ASTM), the American National Standards Institute (ANSI), and the Institute of Electrical and Electronic Engineers (IEEE).

Information contained in calibration procedures should be adequate to enable qualified personnel to properly perform the calibrations. An example of a calibration procedure for mechanical measuring tools appears at the end of this chapter.

A typical equipment calibration procedure includes:

- **purpose and scope;**
- **frequency of calibration;**
- **equipment and standards required;**
- **limits for accuracy and precision;**
- **preliminary examinations and operations;**
- **calibration process description;**
- **remedial action for product; and**
- **documentation requirements.**

Management of Metrology

Managers and administrators should understand the scope, significance, and complexity of a metrology program in order to effectively administer it.

The selection and training of competent calibration personnel is an important consideration in establishing an effective metrology program. Personnel involved in calibration should ideally possess the following qualities:

- **technical education and experience in the area of job assignment;**
- **basic knowledge of metrology and calibration concepts;**
- **an understanding of basic principles of measurement disciplines, data processing steps, and acceptance requirements;**
- **knowledge of the overall calibration program;**
- **ability to follow instructions regarding the maintenance and use of measurement equipment and standards; and**
- **mental attitude which results in safe, careful, and exacting execution of his or her duties.**

Calibration Records

Calibration of each piece of equipment shall be documented to include:

- **equipment identification,**
- **the calibration date,**
- **the calibrator, and**
- **the date the next calibration is due.**

Many manufacturers use a system where each device has a decal or tag which contains the date of calibration, by whom calibrated, and date the next calibration is due. Examples of such decals are shown on the next page.

These decals are examples of the types commonly used to identify the status of measuring instruments and tools. They are available as catalog items or a manufacturer may use its own artwork to purchase decals with specialized wording.

CALIBRATION DATE _____
BY _____

DUE _____

Typical calibration decals have a write-on surface. A tough paper or cloth stock and a pressure sensitive adhesive are used for easy application and removal of the decal. "Due" is the blank for the date when recalibration is due.

CAL. ID No.

Calibration Identification Number or its equivalent is usually the minimum information that may be on equipment. This information allows the manufacturer to read by finding the associated calibration record\card\file.

CALIBRATION VOID

DO NOT USE

Measuring equipment that is not calibrated or otherwise unsuitable for use should be placed in a quarantine area or labeled with a "calibration void" decal.

CALIBRATION
VOID
IF BROKEN

A seal or protective cover for exposed, recessed calibration controls on instruments. The calibration control cannot be adjusted without breaking the seal or removing the instrument case.

NOT A CALIBRATED INSTRUMENT

A decal to be applied to measurement or monitoring instruments not intended for use in determining conformance to device master record specifications with respect to testing, manufacturing, environmental control, etc.

Calibration information is entered onto cards or forms, one for each piece of equipment, or entered into a computerized data system. Most data systems include the calibration date, by whom calibrated, date recalibration is due, the reason for the calibration, comments, address of the manufacturer and calibration laboratory, equipment specifications, serial number, use, etc. An example of a typical card used to record calibration information follows.

CARD# _____ OF _____

CALIBRATION CARD

TYPE _____ MANUFACTURER _____

MODEL _____ SERIAL NO. _____

DATE OF PURCHASE _____ ASSIGNED _____

LOCATION _____ CAL. CYCLE _____

USE ☐ FREQUENT ☐ MODERATE ☐ SELDOM ☐ NOT USED

DATE OF LAST CAL.	REASON FOR CAL. (BROKEN, NORMAL, ROUGH USE)	DATE NEXT CAL. DUE	CAL. INFO. ACCURACY, DEFECTS, LUBE, CLEAN, ETC.

TO BE CALIBRATED BY NAME _____

COMPANY AND ADDRESS _____

PHONE _ _____

FORM #1700 _____

Schedules

Measuring instruments should be calibrated at periodic intervals established on the basis of stability, purpose, and degree of usage of the equipment. Intervals between calibrations should be shortened as required to assure prescribed accuracy as evidenced by the results of preceding calibrations. Intervals should be lengthened only when the results of previous calibrations indicate that such action will not adversely affect the accuracy of the system, i.e., the quality of the finished product.

A manufacturer should use a suitable method to remind employees that recalibration is due. For small manufacturers, calibration decals on the measuring equipment may be sufficient because recalibration can be tracked by scanning the decals for the recalibration date. For other manufacturers, a computerized system, calibration cycle cards, tickler file, or the like may be used. Calibration cycle cards are maintained in a 12-month (12-section) tickler file. There is one card per item of measuring equipment. The cards in the section of the file for the current month are pulled and all of the equipment listed is calibrated. For example, in a 6-month calibration cycle, when an instrument is calibrated in May, the card is moved from the May section to the November section of the file. When the file is checked in November, the cycle card will be there to remind the manufacturer that calibration is due. The process is repeated until an event such as instrument wear-out occurs and the respective cycle card is removed from the file.

Cycle cards are used where a manufacturer has many instruments to be calibrated. It would be rather difficult to keep track of the calibration of a large number of instruments by reviewing calibration record cards or scanning the decal on each instrument. It is easier to use a cycle card file. A cycle card file or equivalent also should be used if the calibration records are filed by type of instrument or manufacturer rather than due date. A typical cycle card follows. The "calibration card number" blank refers to the calibration record card for the same item of equipment.

CALIBRATION CYCLE CARD **FORM NO. 5-15**

MANUFACTURER:_____

INSTRUMENT:_____

_____

MODEL NO._____ **SERIAL NO.**_____

CALIBRATION INTERVAL:_____

LOCATION OF EQUIPMENT:_____

_____

CALIBRATION CARD NO._____

Standards

Where practical, the QS regulation requires that standards used to calibrate equipment be traceable to the National Institute of Standards and Technology (NIST), or other recognized national or international standards. Traceability also can be achieved through a contract calibration laboratory which in turn uses NIST services.

The meaning of traceability to NIST is not always self-evident. Two general methods commonly used to establish and maintain traceability to NIST are:

- **NIST calibration of standards or instruments: When this method is used, private standards are physically sent to NIST for calibration and returned.**

- **Standard Reference Materials (SRM's): NIST provides reference materials to be used in a user's calibration program. These SRM's are widely used in the chemical, biological, medical, and environmental fields.**

Information can be obtained from the "Catalog of NIST Standard Reference Materials," available free from the National Institute of Standards and Technology, Office of Standard Reference Materials,
Gaithersburg, MD 20899, phone: (301)975-2016.

When in-house standards are used, they should be fully described in the device master record or quality system record. Independent or in-house standards should be given appropriate care and maintenance and should be used according to a written procedure as is required for other calibration activities. FDA recommends that at least two in-house standards be maintained -- one for routine use and one for a back up.

Calibration Environment

As appropriate, environmental controls should be established and monitored to assure that measuring instruments are calibrated and used in an environment that will not adversely effect the accuracy required. Consideration should be given to the effects of temperature, humidity, vibration, and cleanliness when purchasing, using, calibrating, and storing instruments.

AUDIT OF CALIBRATION SYSTEM

The calibration program shall be included in the quality system audits required by the QS regulation. These audits should determine the continuing adequacy of the calibration program and assess compliance with the program.

Many manufacturers use contract calibration laboratories to calibrate their measurement and test equipment. If this is the case, FDA views the contract laboratory as an extension of the manufacturer's GMP program or quality system. Normally FDA does not inspect contract laboratory facilities, but it does expect the manufacturer to assess the contract lab to verify that proper procedures are being used. Generally, the manufacturer of the finished device is responsible for assuring the device is manufactured under an acceptable quality system.

When a medical device manufacturer uses a contract calibration laboratory, FDA expects the manufacturer to have evidence that the equipment was calibrated according to the GMP requirements. The device manufacturer can do this by:

- **requiring and receiving certification that the equipment was calibrated under controlled conditions using traceable standards;**

- **maintaining an adequate calibration schedule;**

- **maintaining records of calibration; or**

- **periodically auditing the contractor to assure appropriate and adequate GMP procedures are being followed. For example, the contractor should have:**

    - **written calibration procedures;**
    - **records of calibration;**
    - **trained calibration personnel; and**
    - **standards traceable to NIST or other independent reproducible standards.**

Certification notes and data should include accuracy of equipment when received by the lab to facilitate remedial action by the finished device manufacturer, if necessary. Certification should also include accuracy after calibration, standards used, and environmental conditions under which the equipment was calibrated. The certification should be signed and dated by a responsible employee of the contract lab.

If in-house standards are used by a contractor to calibrate device-related measuring equipment, these standards shall be documented, used, and maintained the same as other standards.

INTEGRATING MEASUREMENTS INTO THE QA SYSTEM

Proper and controlled calibration can contribute to overall quality by assuring that device design and process parameters are accurately measured and that unacceptable items are not accepted, and acceptable items are not rejected as a result of measurements. If the appropriate product-quality parameters are not checked, however, calibrated equipment will have little impact on assuring quality.

A good quality system shall include calibration activities. However, proper calibration will be of little use unless the applications of the measurement equipment are properly developed and qualified during the preproduction development of inspection test methods and procedures. As stated, effectiveness depends on the participation and influence of QA and production management at the preproduction stage. Calibration of equipment cannot correct poor design of products nor can it compensate for poor applications of equipment and techniques. It is the continued use of a complete, integrated quality system, which assures that safe and effective devices are produced.

EXHIBITS

Examples of calibration cards, decals, and cycle cards were presented above in the text. Examples of a device cleaning procedure and a calibration procedure follow. Manufacturers may use these as

presented if they match the manufacturers operations; or may modify them to meet specific requirements.

P.C. Board Cleaning

This procedure covers the cleaning of printed circuit boards by using an automatic washer. The procedure covers operation, shut down, cleaning, and routine maintenance.

Calibration Procedures for Mechanical Measuring Tools

This is a calibration procedure for mechanical measuring tools. In actual use, the initial accuracy of each tool is checked using the procedure and is recorded. Thereafter, each tool is recalibrated (checked) versus the initial accuracy. Of course, the initial accuracy should meet or exceed the requirements of the measurements to be made with the tool. Precision is checked by making several measurements at various points on the tool's measuring face (surface).

TITLE: P.C. Board Cleaning NO:_____
REV:_____ Sheet: 1 of 2

DRAFT: _____ APP: _____ DATE: _____

1.0 PURPOSE: The purpose of this procedure is to document production operations performed on the XXXXXX printed circuit board washer.

2.0 SCOPE: This procedure sequentially identifies all operations necessary to properly operate and maintain this equipment.

3.0 OPERATING PROCEDURES:

3.0.1 Switch the Exhaust Systems fan on.

3.0.2 Assure that the sump pump is on at the circuit breaker panel.

3.1 Turn the power switch to the "ON" position.

3.2 Push the main power "START" button (#21 on Control Panel Diagram).

3.3 Visually inspect all pump compartment and screen filters for debris - make sure they are clean before continuing.

3.4 Push the fill buttons on the rear control panel to fill the wash and rinse sections with water. Make sure all drain lines are closed. The incoming water will stop automatically when the tanks are filled to the correct levels.

3.4.1 Add 4 gallons XXXXXX detergent to the wash tank.

3.5 Depress the center knob on the temperature controllers (#30 on control panel diagram) and turn clockwise until the red pointer indicates 60°C (140°F) for the wash tank and 60° C (140°F) for the rinse tank.

3.6 Wait about 10 min. for water temperature to rise in the wash and rinse tanks. Wait until the red lights on the temperature controllers go off and the black needle aligns with the red pointer.

3.7 Push the START-STOP button (#25 on diagram) on for the conveyer.

3.7.1 Adjust the "SPEED CONTROL" (#27 on diagram) to the correct setting for the boards to be run. See the cleaning specifications for each family of boards for the set points.

3.8 Push the "START" button (#28 on diagram) on for the dryer cycle. NOTE: conveyer belt MUST be moving when dryer section is on or the equipment will be damaged.

3.9 Turn Photocell Switch (on Rear Panel) to the "Automatic" position.

Sheet 2 of 2

4.0 SHUT DOWN PROCEDURES:

4.1 Push the dryer cycle "STOP" button for the Wash and Rinse sections (#29 on control panel).

4.2 Turn Photocell Switch (on Rear Panel) to the "OFF" position.

4.3 Push the conveyer "START - STOP" button (#25 on diagram) to stop the conveyer.

4.4 Pull the DRAIN buttons on the control panel for the wash and rinse sections. Using litmus paper, take a reading on the wash tank before draining it. IF the wash water has a reading of "10" or less drain it; otherwise, do not drain the wash tank. Always drain the rinse tank.

4.5P Pull the FILL buttons on the control panel for the wash and rinse sections to let water flush the equipment for five minutes. Using a soft cloth, wipe off any residue remaining on the equipment.

4.6 Pull the drain buttons on the control panel for the wash and rinse sections to let the water drain.

4.7 Remove the screen filter in the washer and remove any debris.

4.8 Wipe the exterior front section of the machine with a soft cloth.

4.9 Push the main power "STOP" button, (#33) to shut off the equipment.

5.0 MAINTENANCE:

5.1 Monthly

5.1.1 Lubricate the conveyer drive chain with high temperature grease.

5.1.2 Check the wear strips on the conveyer belt frame and replace if required. These are two white plastic strips located at the front of the equipment.

5.1.3 Check conveyer belt tightness - using a wire cutter and needle nose pliers, remove links to tighten if required.

5.2 Quarterly

5.2.1 Shut off power in main panel at rear of equipment.

5.2.2 Lubricate pump motor ball bearing using standard bearing grease.

5.2.3 Lubricate flange bearings on conveyer shafts with bearing grease.

5.2.4 Check all wiring for loose connections and tighten if necessary.

5.2.5 Check all heater contacts - replace worn contacts.

TITLE: Calibration Procedures for Mechanical Measuring Tools No._____Rev._____

ECN Notes _____

_____

Drafted by _____App._____Date_____

PURPOSE: **This procedure establishes a standard method for the calibration and maintenance of mechanical measuring tools such as micrometers, calipers, etc.**

SCOPE: **All measuring tools used to set specifications or measure conformance to specifications, such as micrometers, calipers, etc., will be included in the calibration program. Each tool will be assigned a number and checked every six months for accuracy. If you suspect a tool is damaged or out of calibration, it should be removed from service and brought to the Quality Control Lab (QC) for checking. To enter a tool in the program, take it to QC where a number will be assigned and initial accuracy checked and recorded.**

PROCEDURE:

1. **Each measuring tool shall be kept clean and maintained in a protective container. As needed, all threads and slides shall be lubricated with a fine tool oil to assure free movement.**

2. **The calibration shall be done by a comparison to standard gage blocks traceable to the National Institute of Standards and Technology standard with an accuracy 3 to 10 times greater than that of the measuring tool.**

3. **The comparisons shall be made at different points along the measuring range of the tool. The gage blocks used shall be picked at random to assure that the measuring tool is not checked at the same points on each calibration cycle. When a measurement is made, move the gage blocks from one side of the tool's measuring face to the other on an X/Y axis to assure no wear or taper exists on the measuring faces.**

4. **Measurement tools not intended for testing or manufacturing do not require calibration in accordance with the QS regulation. These tools should be kept out of manufacturing or labeled to avoid inadvertent use. Otherwise, they should be entered in this calibration program.**

5. **After calibration, the date of calibration and the next due date of calibration shall be recorded on the Calibration Form No._____. Any adjustments and/or repairs to be recorded. The form is placed in the tickler file according to the next calibration date.**

6. **If a tool is found to be out of calibration, the QC lab will immediately pass the out-of-calibration information to the appropriate supervisor in the department where the tool is used. The Department and QC management will take appropriate remedial action for affected in-process or finished devices.**

8 DEVICE MASTER RECORDS

INTRODUCTION

Device master record (DMR) is the term used in the Quality System (QS) regulation for all of the routine documentation required to manufacture devices that will consistently meet company requirements. Section 820.3(j) of the QS regulation defines device master record as a compilation of records containing the procedures and specifications for a finished device. The detailed requirements for device master records are contained in section 820.181, as well as throughout the regulation.

The definition for design output in 820.3(g) gives the basis and/or origin of the device master record for all Class II and III devices as follows:

> **Design output means the results of a design effort at each design phase and at the end of the total design effort. The finished design output is the basis for the device master record.**

The total finished design output consists of the device, its packaging and labeling, and the device master record.

For some devices, many of the design output documents are the same as the device master record documents. Other device output information is used to create a DMR drawing such as for a test or an inspection procedure. Figure 6.1 shows the close relationship between design output and the device master record.

Section 820.181, Device Master Record, lists some typical documents in a DMR as follows:

The DMR for each type of device shall include, or refer to the location of, the following information:

(a) Device specifications including appropriate drawings, composition, formulation, component specifications, and software specifications;

(b) Production process specifications including the appropriate equipment specifications, production methods, production procedures, and production environment specifications;

(c) Quality assurance procedures and specifications including acceptance criteria and the quality assurance equipment to be used;

(d) Packaging and labeling specifications, including methods and processes used; and

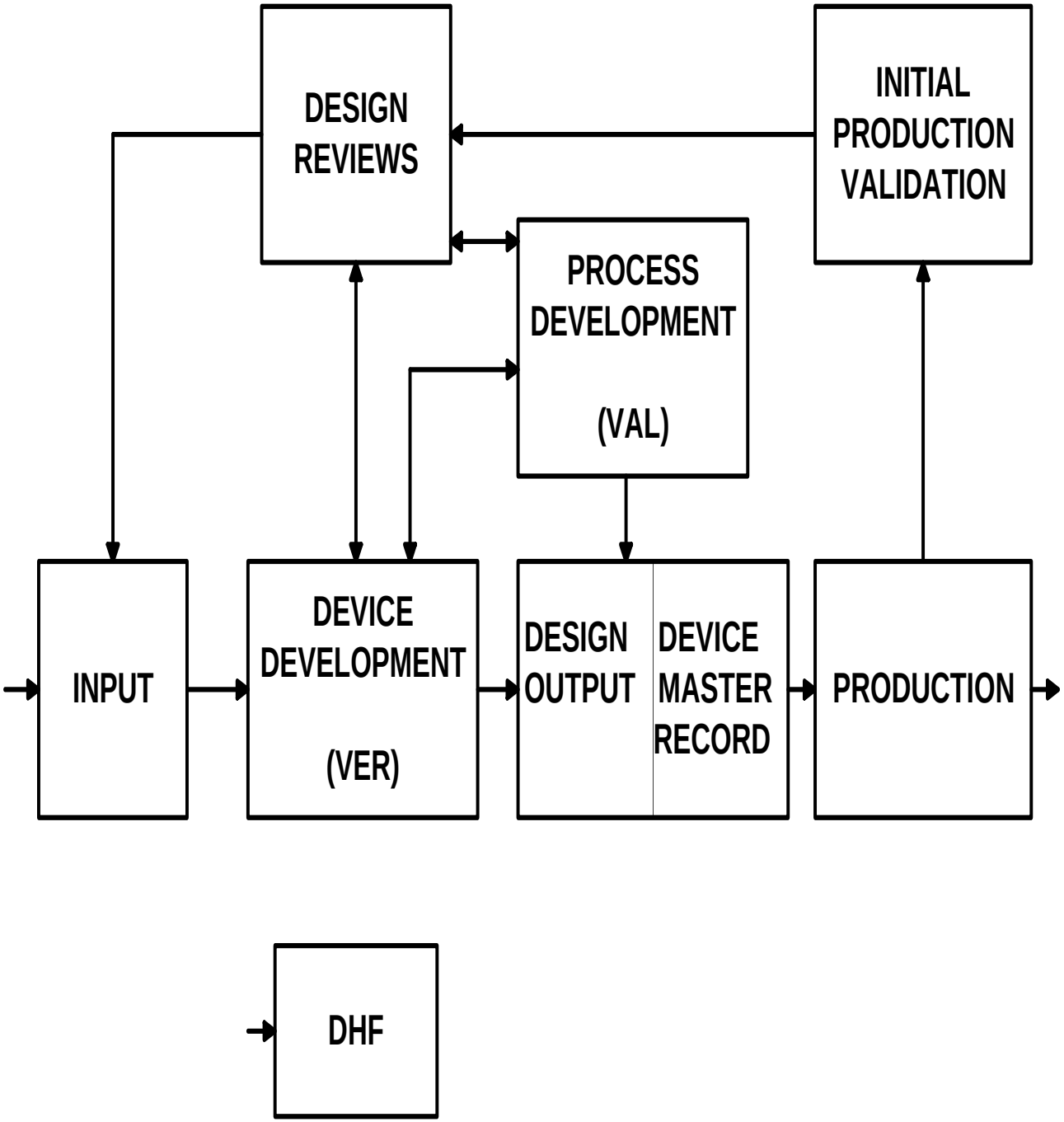
(e) Installation, maintenance, and servicing procedures and methods.

The definition for Design Output 820.3(g) and requirements for Design Output 820.30(d) do not apply to most Class I devices. Therefore, the requirements for the DMR for most Class I devices are in 820.181 Device Master Record. Of course, a manufacturer of Class I devices may use the design output sections of the GMP as guidance.

However, almost all sections of the QS regulation have requirements related to the device master record. The device master record contains specifications for the device, accessories, labeling, and packaging, and contains a full description of how to procure the components and manufacture the device including specifications for facilities, environment, and production equipment. In addition to the device specifications, a device master record contains documents that cover typical manufacturing activities such as:

- **procurement,**
- **assembly,**
- **labeling,**
- **test and inspection,**
- **packaging, and**
- **where applicable, sterilization.**

Note that the listed activities and records or documents are required to produce any product -- medical, industrial, or consumer. There is nothing special about device master records except the name!
Also, note that in common usage, the term "device master record" refers to the total record or any of its individual records. Therefore, the term is singular for the total record, singular for a single document, and plural for a group of single documents. The term also may refer to an original record or a copy of a record.


DESIGN REVIEWS
INITIAL PRODUCTION VALIDATION
PROCESS DEVELOPMENT (VAL)
INPUT
DEVICE DEVELOPMENT (VER)
DESIGN OUTPUT
DEVICE MASTER RECORD
PRODUCTION
DHF

Device master records should be technically correct, contain and/or reflect the approved device and process designs, be under change control, contain the release or other control date, contain an approval signature, and be directed toward the intended user. These requirements are in the QS regulation because the device master record is the "beginning and end" of a product -- errors in the device master record will have a serious impact on the state-of-control of the manufacturing operation and may have a serious impact on the safety and performance of the device. The device master record should be accurate and complete because the essence of the QS regulation is a quality system based on designing a device to meet user needs, documenting the design and production procedures in the device master record and then producing a finished device that meets the device master record requirements. Thus, the device master record shall accurately reflect the device intended to be produced by a manufacturer.

Document For Intended Employees

The content, style, language, graphics, etc., of device master records should be directed toward the needs of the intended employees and, if the record is a specification or text for labeling, it should be directed toward users. A failure to consider the intended user leads to confusion and means that the company has not achieved the state-of-control intended by the QS regulation. Therefore, applicable records should be directed toward the needs of procurement, processing, and test/inspection personnel, rather than the needs of drafting, technical services, or product development departments. Likewise, installation instructions should be directed to installers. Labeling is often prepared by the same employees that draft device master records; and, these employees should also be aware that labeling shall meet the needs of the user as directed by 21 CFR 809.10, 801.6 and 820.30.

In any manufacturing activity such as assembly, labeling, processing, testing, etc., achieving and maintaining a state-of-control is enhanced by appropriate personnel knowing:

- **what task is to be done,**
- **how to do the task,**
- **who is to do the task,**
- **what task is being done, and**
- **what task was done and/or the results of the activity.**

In order for employees to perform a job correctly, they should know exactly what is to be done and exactly how to do the work. Section 820.181 requires that what is done be documented in the device master record. The device master record also contains test and inspection procedures and data forms that are used to help determine and record what was done.

Documents that instruct people how to fabricate, assemble, mix, label, test, inspect, etc., or how to operate equipment should:

- **be directed toward the needs of the employees who will be using them and not directed toward the drafts-person or designer;**

- **match the tools and equipment to be used;**

- **be correct, complete, and current; and**

- **depend on part numbers and basic drawings to transfer information rather than almost photographic type drawings.**

If a component is changed, the representations on pictorial/photographic type drawings are no longer correct and may be very confusing to employees, particularly new employees.

The how-to-manufacture instructions should be adequate for use by the intended employees and correct for the intended operation. In the medium-to-large company, the instructions tend to be extensive technical (engineering) drawings and written procedures. In any company, particularly small manufacturers, the work instructions may take several forms as discussed below.

- **Engineering drawings may be used if employees are trained to read and use them. Some of the how-to information comes from employee training rather than from drawings.**

- **Assembly drawings may contain parts list and quality acceptance criteria. A separate quality acceptance test and/or inspection procedure is not always necessary. An example of an engineering drawing for assembling a handle is exhibited at the end of this chapter. This drawing also includes some of the quality acceptance criteria for evaluating the handle in Notes 1 and 2. The parts list for the handle is on the page after the assembly drawing. Some manufacturers that manufacture simple devices use large sheets of paper for assembly drawings and include the parts list on it. The combination drawing results in instant availability of the parts list and reduces the number of drawings to be controlled. An example of an engineering drawing for assembling a cable and the associated parts list follows the handle assembly drawings.**

- **Exploded-view drawings are used when employees cannot read plan-view engineering drawings. Exploded-view drawings tend to be more "how to" than plan-view drawings. Exploded-view drawings are expensive to draft -- in some cases it may cost less to teach employees how to read and use ordinary plan-view drawings.**

- **Step-by-step written procedures may be used to detail how to perform specific tasks with check-off blanks to show that each specific task was performed. This type of procedure is commonly used for critical operations and where there is little or no visual indication of what has been done, such as for cleaning operations and for mixing chemicals.**

Documentation may be supported by production aids such as labeled photographs, video tapes, slide shows, sample assemblies, or sample finished devices. All of these perform device master record functions and should be identified, and be current, correct, and approved for the intended operation.

The most commonly used aids are models or samples. There are two conditions that should be satisfied in order to use these aids. First, a written specification for the sample shall be contained in the device master record. This specification, of course, may be the same as the specification for the assembly or finished device to be manufactured. This specification shall be subject to a formal change-control procedure. Even though a model is available, the specification is needed for present and future product development, and for production control purposes. Second, the sample should:

- **adequately reflect the device master record specification;**

- **be identified as an approved acceptable representative sample, which means it shall meet the company required workmanship standards; the sample need not be a working model if the nonworking condition is not misleading to employees being guided by the sample; and**

- **when appropriate, contain or be tagged with a drawing number, revision level, and control number (lot, serial, batch).**

A card or tag as shown in the exhibits or an equivalent card may be used to identify and help control the use of samples of assemblies or finished devices. Such tags are usually covered by a clear plastic pouch and attached to the model or sample.

Samples and other aids such as photographs are subject to normal wear and tear in a production environment. Therefore, such aids should be adequately protected by a suitable means such as being located in a protected area, or covered by a protective pouch or container. Production aids should be periodically audited to make sure they continue to be suitable for the intended use. Section 820.100 contains requirements for corrective action. Corrective action may involve the use of samples, changes to the samples, or changes in the control of the samples.

Adequate Information

Although a manufacturer tries to document for the intended employees, there is a need to audit periodically to see how well the goal is being met. There are various means of determining if information in the device master record, production tools, and other production elements are adequate for a given operation and associated employees. These include analyzing the:

- **assistance required by new employees;**
- **assistance required when a new device is introduced into production;**
- **confusion and hesitation;**
- **information exchanged among employees;**
- **"homemade" documentation drafted by the line employees;**
- **rework;**
- **products produced (productivity);**
- **complaints from departments that subsequently process the device; and**
- **customer complaints.**

If any of these factors persist and are out of line with industry norms or with the previous production experience, then the manufacturer should take corrective action. Management shall review the quality system as directed by 820.20 and, thus, be aware of device quality problems or quality system problems such as listed above. The corrective action may include changes in supervision or documentation, adding new documentation, modifying the design, using different tools, modifying the environment, etc.

Preparation and Signatures

A separate device master record is required for each type or family of devices. Also, a separate device master record may be needed for accessories to devices when these are distributed separately for health care purposes. Such accessories are considered to be finished devices. In practice, if the device and accessories are made by the same manufacturer, the device master record for the accessory may be incorporated into the device master record for the primary device.

Within a family of devices, variations in the family may be handled by dash number extensions on drawing and procedure numbers. Usually, a top assembly or other major drawing contains a table/list of the devices in the family and lists the variable parameters for each member of the family.

Section 820.40 of the QS regulation requires that an individual(s) be designated to: review, date, and approve all documents required by the QS regulation including the device master record and authorize changes. An individual(s) with the necessary technical training and experience shall be designated to prepare and control device master records. In addition to requiring approval signatures on device master records, the QS regulation requires individual identification for a few other activities. For convenience, these activities along with the section numbers that require them are listed in Table 8.1.

Table 8.1 GMP ACTIVITIES REQUIRING INDIVIDUAL IDENTIFICATION

820.30(b)	**Approval of Design Plans**

820.30(c)	**Approval of Design Input**
820.30(d)	**Approval of Design Output**
820.30(e)	**Results of Design Review**
820.30(f)	**Results of Design Verification**
820.30(g)	**Results of Design Validation**
820.40	**Approval of in Device Master Record or Changes**
820.70(g)	**Equipment Maintenance and Inspection Activities Performed**
820.72(b)	**Calibration Performed**
820.75(a)	**Approval of Process Validation**
820.75(1)(2)	**Performance of Validated Process**
820.80(d)	**Release of Finished Devices**
820.80(e)	**Acceptance of Activities Conducted**
820.90(b)	**Authorization to Use Non-Conforming Product**
820.120(b)	**Labeling Inspection**
820.180(c)	**Audit Certification**
820.198(b)	**Decisions Not to Investigate Complaints**

The list is self-explanatory except for audit certification. When a manufacturer certifies in writing to FDA that quality system audits have been performed, the certification letter is signed by management having responsibility for the matters audited. Also note that the records in 820.70, 820.72, 820.80, 820.90(b), 820.120(b) and 820.160 are not part of the device master record but, instead, are part of the device history record (DHR). Records in 820.198(b) are part of the complaint files.

If a record that requires a signature is maintained on a computer, it is best if the designated individual(s) maintains an up-to-date signed printout of the record. Where it is impracticable to maintain current printouts, computer-compatible identifiers may be used in lieu of signatures as long as there are adequate controls to prevent improper use, proper employee identification, inaccurate data input, or other inappropriate activity. If identifiers such as coded badges and equipment keys are not controlled (i.e., not restricted to designated employees), then these will not meet applicable GMP "signature" requirements.

Location of Records

Device master records shall be stored at the manufacturing establishment or at other locations (820.180) that are reasonably accessible to company employees responsible for the manufacturing activities and accessible to FDA investigators. Appropriate records may be maintained in computer data banks if the records are protected, change controlled, and readily accessible for use by responsible employees at all relevant facilities. It is acceptable for a manufacturer to maintain records on microfilm and discard the original hard copies. Microfiche and/or microfilm reductions may be used in lieu of original record retention if the following conditions are met.

- **All reductions shall be readily available for review and copying by FDA investigators and designated company personnel at any reasonable time.**

- **All necessary equipment shall be provided for viewing and copying the records.**
- **Reproductions shall be true and accurate copies of the original record.**

If the reproduction process results in a copy that does not reveal changes or additions to the original record, the original should be retained. In this situation, the reproduced copy and any image shown on a viewing screen should note any alteration from the original and indicate that the original record is available.

By maintaining the device master record, complaints and other records required by the QS regulation at the manufacturing establishment or other reasonably accessible location, responsible officials of a company can exercise control and accountability over the entire design, manufacturing, and postmarketing activities and, thereby, maximize the probability that the finished device conforms to its design specifications. This GMP requirement helps assure that responsible officials at the manufacturing establishment have ready access to those documents essential for producing devices and for conducting self-inspections, complaint investigations, failure analyses, audits, and corrective action.

The device master record is a single source document or file. Portions of this file may be kept in various locations. A device master record may exist as:

- **one or more files or volumes of the actual records containing the information required by the QS regulation;**
- **a reference list of such documents and their location; or**
- **any combination of actual documents and/or reference lists.**

These documents shall contain the latest DMR revisions, be signed, and be dated to show they have been checked for adequacy and approved for use (820.30, 820.40 and 820.181).

The QS regulation allows use of reference lists as a means to reduce the duplication of records, particularly duplication of general documents such as standard operating procedures (SOP's). General SOP's (not directly related to a product or process) however should be made a part of the quality system record (QSR) (820.186).

Use of a reference list also allows filing of device master record documents at several convenient locations. If the device master record contains a list of documentation, the actual documents shall be available for employee use and FDA inspection at the manufacturing site or other reasonably accessible locations. As noted above, this is a key and important GMP requirement. Typical locations of various device master records are shown in Table 8.2.

When performing an inspection of a company, FDA investigators shall have access to actual records for review and copying during reasonable business hours. FDA investigators review these records to determine if a manufacturer is complying with the QS regulation and with the Food, Drug, and Cosmetic Act.

Records deemed confidential by a manufacturer should be marked to aid FDA in determining whether or not specific information may be disclosed under the Freedom of Information Act. However, routinely stamping every document as "Confidential" defeats the purpose of requesting extra care be taken to protect a specific document or set of documents.

Table 8.2 LOCATION OF DEVICE MASTER RECORDS

	Typical Locations of Documents	
TYPE OF DMR ELEMENT	**ORIGINALS**	**WORKING COPIES**
Reference list(s)	**Engr. master file**	
Component drawings	**Engr. or Manuf. Engr.**	**Manuf. or Procurement**

	master file	
Component acceptance procedures	**SOP master file**	**Receiving department**
Device Input specifications (final version)	**Engr. master file**	**Marketing or Engineering**
Manufacturing procedures	**Engr. or Manuf. Engr. master file**	**Manufacturing**
Test specifications	**Engr. master file**	**Engr. or Manuf. Engr.**
Test procedures	**Engr. or Manuf. Engr. master file**	**Manuf., QA, QC or Final Test**
Inspection procedures	**Manuf., QC, or SOP master file**	**Manufacturing or QC**
Label drawings	**Engr. master file**	**Engr., QA, or Manuf.**
Label artwork	**Artwork master file**	**Engr., Procurement**
Label control procedures	**Manuf., QC, or SOP master file**	**Manufacturing**
Specific cleaning procedures	**SOP master file**	**Manufacturing**
General cleaning procedures	**QSR master file**	
System audit procedures	**QSR master file**	
Employee training procedures	**QSR master file**	

SOP = Standard Operating Procedure
QSR = Quality System Record
QA = Quality Assurance
QC = Quality Control

Record Retention

The QS regulation in section 820.180(b) requires that all records pertaining to a device shall be retained for a period of time equivalent to the design and expected life of the device, but in no case less than two years from the date of release for commercial distribution by the manufacturer. Manufacturers of long-life products should make prudent decisions as to how long to keep records. For example, there may be no value in keeping records for long-life devices such as stretchers, surgical tools, containers, etc., forever if the probability is low that any post-distribution remedial activity will occur. For devices that require repair or capital equipment devices that probably will be updated, appropriate records should be retained to support these repairs or modifications.

Device master record requirements apply to devices modified in the field by the manufacturer's representatives after the devices are commercially distributed. Modification of a device is manufacturing and the QS regulation covers all manufacturing of devices where the result is placed into commercial distribution. In any case, a manufacturer should be prepared to provide a rationale for its decision to discontinue record-keeping.

DEVICE MASTER RECORD CONTENTS

As discussed above, the device master record shows and/or tells employees how to perform specific functions related to the production of a device. The QS regulation does not dictate how this information is to be arranged or filed in the device master record and quality system record except that it shall be readily accessible. Because each device master record and quality system record contain many documents, an index of each is usually needed.

Device Specification

There may be many specifications in the device master record. One of these is the device specification. A device or product specification is a specific document in the device master record that briefly describes and gives all important details of the external characteristics of a device. The product specification may also contain some internal characteristics of the device that are important to the manufacturer and/or the users. The finished device specification is derived from the design input specifications in 820.30. For some devices, many of the external characteristics such as temperature tolerance are related to the environment in which the devices will function properly. For some in vitro products, the package insert is used by some manufacturers as the product specification for marketing purposes.

Generally a product specification will contain the device's:

- **product trade and common name(s);**
- **intended use(s);**
- **performance characteristics and theory of operation;**
- **regulatory classification;**
- **physical characteristics;**
- **environmental limitations and product stability;**
- **important components and formula (if applicable); and**
- **user safety characteristics.**

Table 8.3 contains a list of characteristics that often appear in product specifications; however, note that not all of the listed items will appear in the product specification for a given device.

In addition to defining and describing a device, a product specification is a communication tool which, if used in a timely manner, can help achieve some important results. First, it helps assure that everyone is talking about the same device and working toward the same objectives with respect to safety, effectiveness, human factors, configuration, labeling, packaging, processing, finished device acceptance, etc.

Ultimately, the device specification or a condensed version of it should be used in catalogs, or other product documentation, to aid communication between salespersons and customers. If the marketing department uses the product specifications when preparing advertisements and catalog sheets, public relations with users will be enhanced because the marketing documents are based on proven scientific safety and performance claims for the actual device. The user has an opportunity to read the technical specifications of the item actually being offered for sale.

Thus the use of device product specifications will result in:

- **improved communication between employees on a departmental and interdepartmental basis;**
- **less confusion and increased morale;**
- **an improved state-of-control;**
- **a higher probability of meeting cost, time, safety, effectiveness, and regulatory compliance objectives; and**
- **product literature that correctly describes the device for the prospective customer.**

A sample product specification for a portable defibrillator is in the exhibits at the end of this chapter. This specification is long and detailed because it is a combined product and test specification, and because it is for a complex device.

Specific Documents

Specific documents are drawings, procedures, labels, data forms, etc., for a specific product or family of products. Product specific documents are almost always part of the device master record. The originals of specific documents are usually located in files in engineering or technical service departments. In most manufacturers, specific documents contain no general information; however, they often refer to general documents. (A list of specific and general documents is exhibited later in this chapter.) The number of specific documents for a given product line may range from about 10 to several hundred. If large numbers of documents are needed, an index is usually needed to help locate them, particularly for personnel that do not work in the drafting department or in technical services.

Records for In Vitro Diagnostic Products

The main differences between device master records for chemical-based in vitro products and for electromechanical products, such as instruments and artificial kidneys, is terminology and the relatively extensive use of written processing procedures and status reports for in vitro diagnostic products rather than a few assembly drawings and test/inspection reports. For example, device master records for chemical-based devices would contain a manufacturing section dealing with areas such as solution preparation and filling, whereas manufacturing sections for electromechanical products would cover operations such as assembly. Status records for weighing, mixing, filling, etc., are used for general control of in vitro products. Status reports are also used because it is often difficult to determine the status of in-process in vitro products by looking at them -- the opposite is usually true for most hardware devices. Records for in vitro devices also shall contain control data that allows components and kits to be traced [809.10(a)(9), etc.].

Table 8.3 ITEMS THAT MAY APPEAR IN A DEVICE SPECIFICATION

1. Name of Product

- **a. Trade name**
- **b. Trademark**
- **c. Generic name**
- **d. Chemical name**
- **e. Official name**
- **f. Common name**

2. Performance Characteristics

- **a. Description/Intended use**
- **b. Accessories**
- **c. Functional parameters**
- **d. Limitations**
- **e. Contraindications**
- **f. Input/Output requirements**
- **g. Human interface**
- **h. Other**

3. Classification

- **a. Regulatory**
- **b. Commercial**
- **c. Functional**
- **d. Other**

4. Physical Characteristics

- **a. Weight**
- **b. Size f. Packaging**
- **c. Color**
- **d. Form/Shape**
- **e. Consistency**
- **g. Power requirements**
- **h. Other**

5. Environmental Limitations

- **a. Operating temperature range**
- **b. Storage temperature range**
- **c. Vibration and shock range**
- **d. Voltage range**
- **e. Humidity range**
- **f. Moisture protection**
- **g. Pressure, altitude limits**
- **h. Electromagnetic interference**
- **i. Electrical transients**
- **j. Shelf life/Other**

6. Important Components

- **a. Active ingredients**
- **b. Major subsystems**
- **c. Diagnostic kit materials**
- **d. Accessories**
- **e. Labeling**
- **f. Service labeling**
- **g. Components/items supplied by user**
- **h. Software**
- **i. Periodic Warranty/Other**

7. User Safety and Performance Considerations

- **a. Chemical**
- **b. Electrical**
- **c. Thermal**
- **d. Mechanical sharp, moving parts**
- **e. Personnel training**
- **f. Periodic testing**
- **g. Maintenance**
- **h. Other**

QUALITY SYSTEM RECORD DOCUMENTS

Quality system record (QSR) (820.186) or general documents are used for many activities that are essential to operating a manufacturing establishment -- these are not specific to any given product even if the company produces only one product. Thus, the quality system record includes general documents such as standard operating procedures (SOP's) and standard quality assurance procedures (QAP's). If the company added another product line, the basic content of these documents would undergo none or only minor changes.

In a typical manufacturing operation, general QSR, SOP, and QAP documents may include the following:

Employee training procedures
Cleaning procedures
Insecticide use-removal procedures
Air conditioning/heating procedures
Tool kit policy
Safety procedures
Procurement procedures
Returned goods policies
Drawing numbering system
Change control procedure
Service policy
Supplier assessment policy
General design control procedures
Component inspection procedures
Workmanship standards
Design review policy/procedure
Label review policy/procedure
Sterile water system maintenance
Calibration policy
Complaint handling procedure
Recall procedure
Deviation review policy/procedure

The above list is not all inclusive. Medium-to-large companies tend to have many of these general documents to guide management in maintaining consistent operations. A very small company may have only the most essential and appropriate of these documents such as procedures for design controls, drawing numbering system, change control, employee training, use of hazardous materials, etc.

The original copy of each general procedure is filed in the department specified by management as having responsibility for maintaining that procedure, or it is filed in an automated system with access by the designated departments. The working copies of the above procedures are usually located in SOP manuals and QA manuals. The procedures are usually numbered and arranged in a logical order by topic. The QS regulation does not require manufacturers to keep quality system record documents in SOP or QA manuals; however, the experience of many industries has demonstrated that such manuals are worthwhile if they are kept current and contain only the real working procedures.

WRITTEN PROCEDURES

Many sections of the QS regulation require written procedures for instructions in performing various quality system, design product acceptance, QA, and manufacturing tasks. Certain devices such as in vitro products, because of the nature of the manufacturing operations, tend to have a relatively large number of written procedures.

Written procedures are used for quality system audits, product development, manufacturing, post-marketing activities, etc., to:

- **improve communication and guidance;**
- **assure consistent and complete performance of assigned tasks; and**
- **promote management of operations.**

In large manufacturing facilities involving many operations and people of various skill levels, many written procedures are usually necessary. In a small manufacturer, communication lines are usually short, few people are involved, and management is readily available to provide guidance, so that the need for written procedures is usually less than for a larger manufacturer.

A manufacturer, particularly a small manufacturer, may conclude that GMP requirements for written procedures are not applicable for a particular operation. Although the number of written procedures may vary, all manufacturers are required to maintain a device master record (820.181) for each type or family of devices they produce.

Often training and work experience alone or combined with drawings, photographs, and models are valid substitutes for written procedures. For example, machinists are typically skilled personnel who fabricate components and finished devices using dimensional drawings for guidance instead of written procedures. The company and FDA investigator will evaluate each situation based on the training and knowledge of the operators and the control needed to meet device specifications. Typically, a written procedure is not necessary when:

- **the activity is very simple;**
- **the activity is relatively simple and models are used as production aids;**
- **straightforward quantitative rather than qualitative standards determine acceptability; and**
- **the operation is performed by personnel highly skilled relative to the task being performed.**

Written procedures and associated history or status records, however, are often needed for activities where there is no change, such as color, texture, or form, to indicate that the activity has been performed correctly.

Manufacturers should determine that they meet all GMP requirements and, if necessary, exceed them in order to produce finished devices that meet device master record specifications because FDA insists that manufacturers meet their quality claims [FD&C Act, section 501(c)]. Achieving this required state-of-control may require fewer or more written procedures than specifically required by the QS regulation. FDA does not insist that a manufacturer generate records that do not contribute to assuring conformance to specifications.

Developing Procedures

Developing written procedures is relatively labor intensive and time consuming, which may lead to use of "back-of-the-envelope" notes instead of formal procedures. Likewise, changing these procedures is time consuming, which may lead to delays or forgetting to make the changes. Drafting or changing written procedures is also prone to errors. Therefore, manufacturers are encouraged to use computers and low-cost printers as word processors to aid in writing and changing procedures. With the use of computers, these tasks become easier thereby increasing the probability that they will be performed correctly and when needed. Computers can also be used for generating and maintaining device master record indices and complaint files, and performing a host of other GMP related activities.

There is a method for developing procedures that will result in short, clear procedures that help

solve real problems. The first two steps are:

- **identify the problems to be solved; and**
- **decide if new or modified procedures are needed to help solve or reduce the problems.**

Events that point to a problem are excessive rework, employee confusion, customer complaints, recalls, etc. These "pointers," however, may not be the real problem. The real problem may be inadequate design, components, equipment, maintenance, operational techniques, documentation, environment, etc. The real problem should be identified before it can be solved. A written procedure may or may not be needed to help solve the problem.

The real problem can be identified by careful analysis of:

- **the "pointers" noted above,**
- **device design,**
- **process design,**
- **process flow and employee work habits (operational analysis),**
- **test and inspection data, and**
- **any other activity related to the quality of the device.**

Operational analysis is aided by flow-charting which is a step-by-step chart of the minute details of the operation. Thus, a flow chart is much more detailed than a QA audit report and is very helpful in determining what is actually happening in a particular manufacturing operation. This knowledge may lead to a solution of manufacturing and quality problems. An example of a flow chart appears in the exhibit section of chapter 10.

From a company quality system, interface, and personnel management viewpoint, the problem, the reason for flow-charting the given activity, etc., should be discussed with affected personnel. Their input should be requested with respect to identifying and solving the real problem. By using the information presented by the flowchart and the experience gained while producing the chart, the QA auditor is better able to:

- **analyze the particular operation with respect to process requirements;**

- **determine what needs to be added, modified, or deleted to solve any problems or improve performance; and**

- **if needed, write or modify a procedure to cover the new way of performing the activity.**

Content of Procedures

Written procedures are widely used and industry experience has shown that these should contain the following items:

- **company identification and a procedure title;**
- **an identification or control number with a revision level code;**
- **an approval signature, and date the procedure becomes effective;**
- **the number of pages (e.g., sheet 1 of 4) in the procedure or another means to indicate that the employee has the complete document; and**
- **step-by-step instructions for performing the required activities**

The effective date may be the same as the approval date. Also, the effective date may appear on a separate document such as an engineering change order (ECO) form. The main body of the procedure should cover, as appropriate:

- **subject, scope, and objectives;**

- **who is assigned to perform the task;**
- **what activity or task is to be performed;**
- **when and where the task is to be performed; and,**
- **how to perform the task including what tools, materials, etc., to use.**

Particularly for the new employee, it is important for the procedure to state the reason for performing a function and the reason it is to be performed in a certain way. Background information such as this helps the employee to understand an assignment and remember how to perform it. For example, when working on static sensitive integrated circuits that are easily damaged by electrostatic potentials, unskilled employees need to understand why they have to be grounded, work on grounded mats and, especially, why they are not allowed to wear certain fabrics while at work. Likewise, employees working in environmentally controlled, clean manufacturing areas need to be told about invisible microbes and particulates, and that humans are the major source of these unwelcome contaminates. If so informed, employees are more likely to follow the operational procedures for working in controlled areas.

The task description in each procedure should cover appropriate details such as:

- **the expected and actual results from performing the tasks, such as what data to collect and how to analyze, file, and report it;**

- **what to do with the component, in-process device, or finished device if such is involved; and**

- **any related activities that need to be performed in order for the overall operation to remain in a state-of-control or for the device to meet the company device master record specifications.**

If the procedure being developed, for example, covers change control, the procedure should also cover related activities such as changes to labeling. Consider a change to a device where an analog meter is replaced with a digital meter -- obviously the instruction manual (labeling) and service manual also need to be modified. Otherwise the finished device:

- **may not meet company labeling policies;**

- **is misbranded because it does not meet the labeling requirements of the FD&C Act; and,**

- **is adulterated because the change does not meet the change control requirements of the QS regulation.**

After the procedure is drafted, if appropriate, it should be reviewed with the affected personnel before it is approved and implemented. During the initial implementation, the use of the procedure should be monitored. Then, based on actual experience in using the procedure, if necessary, it should be modified to more exactly meet the need of the operation or process.

CHANGE CONTROL

The QS regulation in section 820.181 by reference to 820.40 requires that any changes to the device master record be authorized by the signature of a designated individual(s). Change control requirements also appear throughout the QS regulation. The control of changes to devices, processes, and the associated device master records is one of the most important

elements of a quality assurance system. The requirements for a successful change control system are so extensive that the entire next chapter of this manual is devoted to changes and associated procedures.

EXHIBITS

Reprinted on the next pages are typical documents (records) that appear in device master records. Manufacturers may use these as guides in developing their device master records.

Documents That May Appear in a Device Master Record

The first exhibit is a list of documents that might appear in device master records. Each device master record would contain only those documents that are applicable for a specific device. Some of the listed documents are general rather than product specific. General documents are usually called standard operating procedures (SOP's) and, if necessary, are referenced in the device master record rather than actually being included. The general documents are usually part of the quality system record (QSR).

Device Master Record Index

This exhibit is a policy/procedure for drafting a device master record index. An index is also known as a document plan, table of contents, etc. An example of a device master record index follows immediately after the policy/procedure. Note that this particular policy/procedure contains definitions. It is important that procedures contain definitions, in a case like a complex device master record index where employees may not be familiar with the terminology.

Product Specification for a Portable Defibrillator

Finished device or product specifications are the backbone of any device master record. The one illustrated as the third exhibit is for a complicated piece of equipment and is, therefore, extensive. For long documents it is recommended that a table of contents be incorporated as was done in this specification. Appendix A and B of this specification are not exhibited.

Zener Diode Specification

This specification for a non-complicated part contains the necessary information to describe the item in sufficient detail for the correct part to be procured per the 820.50 Purchasing Controls.

Label Example

A sample label is exhibited. Labels and labeling are components and their specifications, art work, etc., are part of the device master record. As for any component, labeling shall be specified (documented). The resulting device master record document shall be reviewed, approved, change controlled, and stored such that it may be readily accessed. Such records are used to meet requirements such as those in 820.50, 820.80(b), 820.80(d), 820.120(b), 820.120(e), etc.

Handle Assembly and Parts List

This exhibit is an engineering drawing and parts list for a handle assembly. Engineering drawings, parts lists, or formulations are a vital part of many device master records. In this case, the engineering drawing not only details how this assembly is to be made, but there is also important information in the notes on the drawing. If properly trained and with sufficient experience, employees are able to use this drawing as the instructions for assembly of this handle. A written assembly procedure is not necessary.
Cable Assembly and Parts List

This exhibit is similar to the handle assembly mentioned above. The type of drawing used and information on a drawing can aid a manufacturer in reducing paperwork needed to manufacture a specific product.

Device Master Record Index for Amylase

This document is a device master record index for an in-vitro diagnostic product. Proprietary information in this index is replaced by X's. The company that prepared this index uses purchase specifications and raw material specifications. Some manufacturers, particularly small companies, specify and purchase standard, routine items such as bottles and caps by using catalog numbers. Component specification drawings are not always used for routine items such as standard bottles.

Product Description

This exhibit is a product description for an in vitro diagnostic product. The standard operating procedures, quality control procedures, manufacturing flow sheets, and notes mentioned in this product description are not reprinted herein.

Amylase Diluent Solution

This exhibit is the procedure for making a batch of amylase solution. In this procedure, note that for each step the company requires the initials or signature of the person actually performing the operation and of the individual who checked that person's performance of the operation.

Filling Record - Liquid, Non Freeze Dried

This is an exhibit of a filling record used for liquid products to document the steps in a filling operation. The completed filling record becomes a part of the device history record (DHR) for the batch being filled.

Finished Product Release Form

This form is used to record that the device history record is complete for a lot of product, the product meets specifications, and the lot may be approved for release.

Production Sample Card

This exhibit shows both sides of a card or tag used to identify and help control the use of manufacturing aids such as samples of assemblies or finished devices. The use of a sample identification card is described in the main text of this chapter.

Shop Order Traveler

The last exhibit is two job travelers or job followers. These cards, forms, tags, etc., are used to identify a batch or sub-batch of in-process assemblies as they are passed from one department to another. Where needed, travelers are used to reduce mixups and confusion and, in general increase the state-of-control of an overall manufacturing operation. Travelers help meet the general requirements of 820.60, Identification, and the specific requirements of 820.86, Acceptance Status.

DOCUMENTS THAT MAY APPEAR IN A DEVICE MASTER RECORD

1.0 Device Master Record Index

The device master record Index is a table of contents which is used for convenience. It may be known as a:

Device Master Record Index
Documentation or Device Master Record Unit;
Documentation Plan;
Product Tree;
Documentation Index;
Product Structure; or
Bill of Materials (if it also lists the device master record documents).

2.0 Device Specifications

(Device specifications are described in the chapter text.)

3.0 Manufacturing Information

3.1 Index
(Optional. See 1.0 above for total table of contents.)

3.2 Formulation or top assembly drawing

3.3 List of components

1. **List of ingredients (including grade or type)**
2. **Bill of materials (i.e., component list usually arranged by subassembly or other sub-product level or by process steps)**
3. **Formula**

3.4 Procurement documentation

1. **Specifications**
2. **Drawings**
3. **Certificate of compliance requirements**
4. **Supplier Assessment procedures**

3.5 Device documentation

1. **Fabrication drawings**
2. **Surface finish procedures**
3. **Subassembly drawings**
4. **Wiring and piping diagrams**
5. **Assembly procedures**
6. **Assembly drawings**
7. **Reference documentation**
   - **a. Wiring and piping schematics**
   - **b. Test specifications**
8. **Sub-batch procedures**
9. **Blending or mixing procedures**
10. **Solution procedures**
11. **Final formulation procedures**
12. **Software packages**

3.6 Precautions and special notations

1. **Apparel**
2. **Cleaning**
3. **Storage conditions**
4. **Filling, mixing conditions**
5. **Hazards and safety precautions**

3.7 Equipment, lines, and procedures

1. **Process lines**
2. **Assembly lines**
3. **Vessels**
4. **Mixers, tools**
5. **Molds**
6. **Machine maintenance procedures**
7. **Calibration procedures**
8. **Setup procedures**
9. **Operating procedures**
10. **Process flow charts**

3.8 Sterilization procedures

1. **Procedures for ethylene oxide, radiation, filtration, steam, etc.**
2. **Handling and flow procedures**
3. **Cycle parameter specifications**
4. **Diagrams for loading products in the chamber**

3.9 Production control documentation

1. **Inspection procedures**
2. **Test procedures**
3. **Blank job travelers**
4. **Blank inspection/test forms**
5. **Instrument charts**
6. **Reporting forms**
7. **Approved deviations**

4.0 Labeling and Packaging

4.1 Index (Optional. see 1.0 above.)

4.2 Labeling

1. **Label drawings**
2. **Labeling drawings**
3. **Label/labeling review procedures and forms**
4. **Production control procedures and history record forms**
5. **Instruction manuals**
6. **Service manuals**
7. **Customer software**
8. **Customer feedback forms**

4.3 Packaging

1. **Package drawings (usually includes labeling information)**
2. **Closure drawings**
3. **Filling and/or packaging procedures**
4. **Packing procedures**
5. **Special shipment procedures**

4.4 Storage requirements

1. **Temperature**
2. **Humidity**
3. **Shelf-life**

5.0 Control Procedures and Activities

5.1 Index (optional. see 1.0 above.)

5.2 Inspection procedures

1. **Incoming**
2. **In-process**
3. **Finished devices**
4. **Process control charts**
5. **Blank data reporting forms**

5.3 Test procedures

1. **Incoming**

2. **In-process**
3. **Pretest conditioning**
4. **Finished device**
5. **Process control charts**
6. **Blank device history record forms**
7. **Automated test programs and/or software**

6.0 Final Release

6.1 Release document review list

6.2 Distribution procedures

6.3 Blank device history record forms

Title: DEVICE MASTER RECORD INDEX

Policy No._____ Rev._____ **Date_____**
Approval _____

1.0 Purpose and Scope: To prescribe the responsibilities for preparing device master record (DMR) Indices and content of DMR Indices (lists).

2.0 Policy: A DMR Index shall be prepared and maintained for all devices being developed or manufactured.

3.0 Definition: A DMR Index is a table of contents for the device master record of a device. It also contains information on the breakdown of the device into assemblies and/or manufacturing steps. It is called a document plan during planning and early development of a new product. A DMR is:

3.1 An aid in proposing, planning, tasking, and reviewing projects;

3.2 A framework for preparing drawings, parts lists, and test equipment lists;

3.3 A means of familiarizing personnel with the device configuration;

3.4 A current record and status of the physical configuration of the device and a list of all reference documentation required; and

3.5 An index to the product-specific documentation required for procurement of components, manufacture, and evaluation of a device.

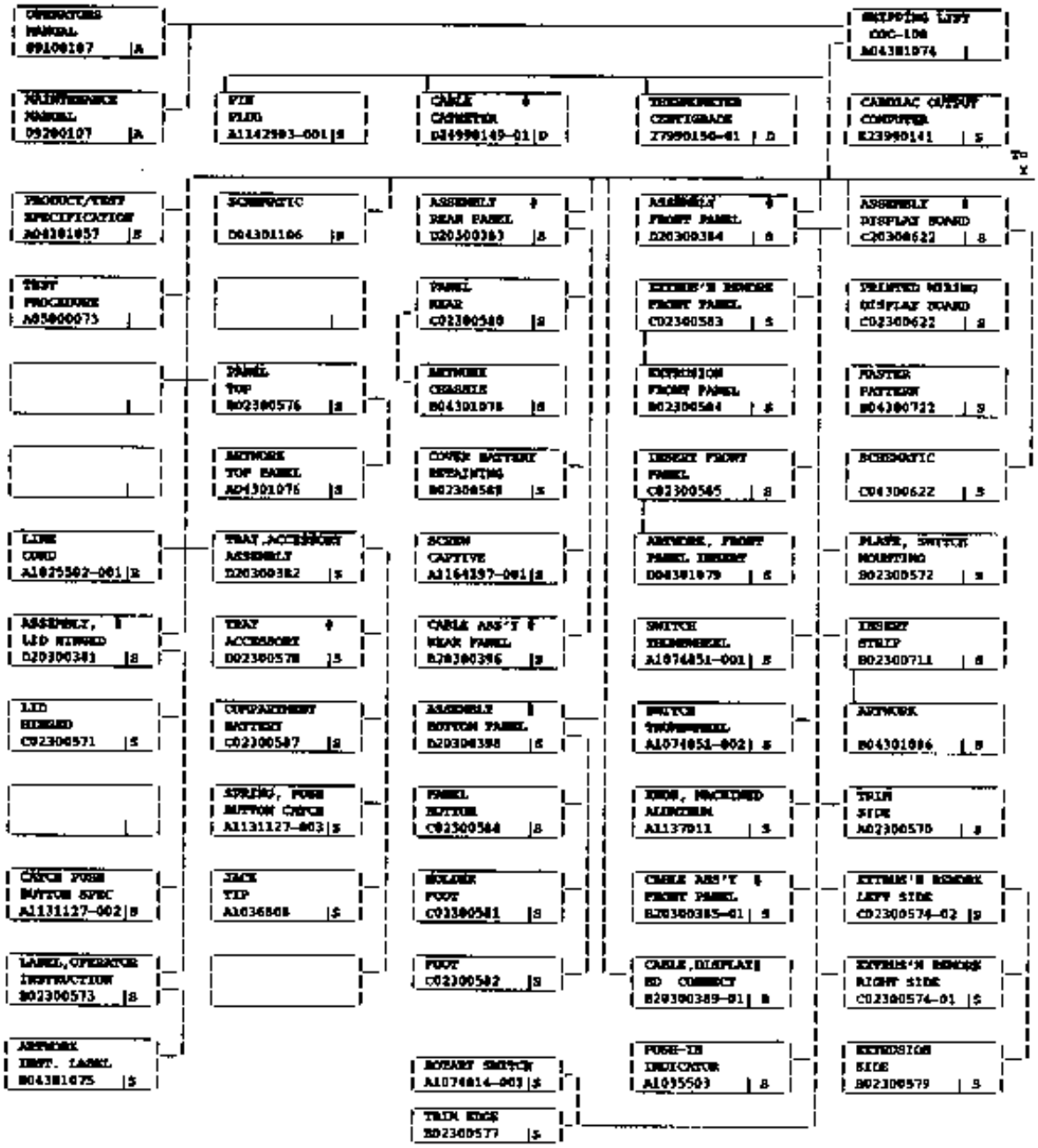
4.0 Procedure:

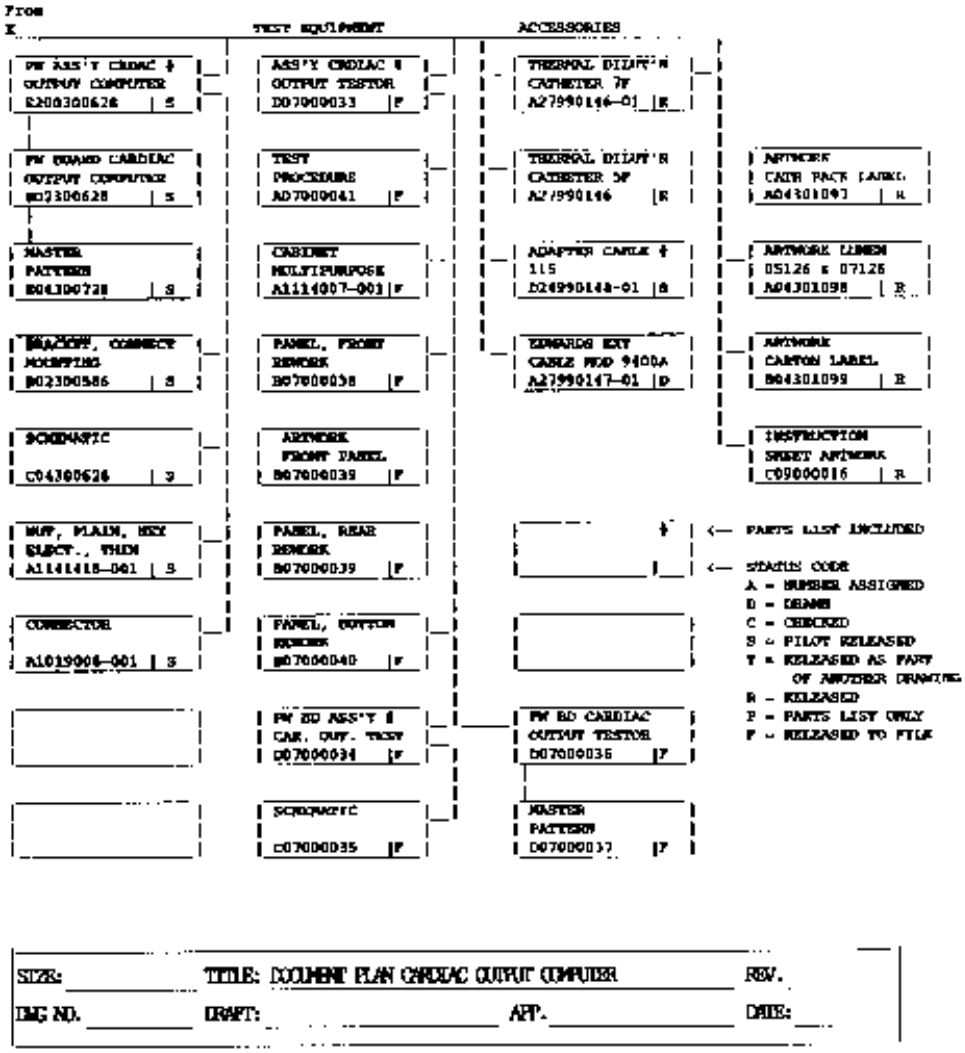
4.1 Preliminary document plans may be generated for the convenience of Engineering. Upon completion of the design when formal records are needed, a formal document plan will be initiated.

4.2 The configuration and structure of the document plan is set by the Engineering, Manufacturing Engineering, and Drafting Supervisors.

4.3 After agreements, the plan will be drawn, document numbers assigned, status of drawings indicated, and the plan approved by Engineering and Manufacturing. All non-product specific documents such as standard operating procedures that are used during production of the device will be listed on the plan. (Because the plan is now complete, it is a DMR Index.)

5.0 Example: Part of an index in "tree" form is on the following pages. A "tree" form allows a large amount of information to be displayed in a small area. Each column covers a major section of the documentation such as the battery charger. The index contains codes to convey additional information such as a rectangle with a dark triangle in a top corner or a mark such as "#" to indicate a parts list is included with a particular drawing.




From K
TEST EQUIPMENT
ACCESSORIES
PW ASS'Y CRDAC & OUTPUT COMPUTER 8200300626 S
ASS'Y CRDIAC & OUTPUT TESTOR D07000033 F
THERMAL DILUT'N CATHETER 7F A27990146-01 R
PW BOARD CARDIAC OUTPUT COMPUTER 8023006628 S
TEST PROCEDURE AD7000041 F
THERMAL DILUT'N CATHETER 5F A27990146 R
ARTWORK CATH PACK LABEL A04301097 R
MASTER PATTERN 804300728 S
CABINET MULTIPURPOSE A1114007-001 F
ADAPTER CABLE & 115 D24990148-01 S
ARTWORK LINEN 05126 & 07126 A04301098 R
SCHEMATIC, CONNECT MOUNTING 8023006586 S
PANEL, FRONT REMARK B07000038 F
EDWARDS EXT CABLE MOD 9400A A27990147-01 D
ARTWORK CARTON LABEL 804301099 R
SCHEMATIC C04300626 S
ARTWORK FRONT PANEL B07000039 F
INSTRUCTION SHEET ARTWORK C09000016 R
MUF, PLAIN, HEX SOCKT., THDD A1141418-001 S
PANEL, REAR REMARK B07000039 F
<— PARTS LIST INCLUDED
<— STATUS CODE
A = NUMBER ASSIGNED
D = DRAWN
C = CHECKED
S = PILOT RELEASED
T = RELEASED AS PART OF ANOTHER DRAWING
R = RELEASED
P = PARTS LIST ONLY
F = RELEASED TO FILE
CONNECTOR A1019006-001 S
PANEL, OUTPUT REMARK B07000040 F
PW BD ASS'Y & CAR. OUT. TEST D07000034 F
PW BD CARDIAC OUTPUT TESTOR D07000036 F
SCHEMATIC C07000035 F
MASTER PATTERN D07000037 F
SIZE: TITLE: DOCUMENT PLAN CARDIAC OUTPUT COMPUTER REV.
DWG NO. DRAFT: APP. DATE:

8 26

(Sample for training purposes only. Do not use for technical parameters.)

PRODUCT SPECIFICATION PORTABLE DEFIBRILLATORS

CONTENTS

Throughout this Product Specification * indicates need for test.

NOTE: Values not in parentheses refer to Models D320 and D320W. Values in parentheses refer to Models D400 and D400W.

LTR	DESCRIPTION	DATE	APPROVED
1	Pilot released per ER - 3556	04/23/75	
2	Revised and Retyped per ECO - 3968	01/27/76	
3	Revised and Retyped per ECO - 4225	05/28/76	
4	Revised per ECO - 4636	12/28/76	
A	Released to Production per ERN - 4645	03/10/77	

Title: PRODUCT SPECIFICATION PORTABLE DEFIBRILLATORS

DR BY: A J Lucas	**DATE: 4/15/75**	**DWG NO. 04300538**	**Sheet 1 of 14**
		REVISION: A	**Date: 3/10/77**
APP'D: _____	**DATE: _____**		

D320, D320W, D400, & D400W

1.0 REFERENCE DOCUMENTS

1.1 Portable Defibrillators D320/400 and D320W/400W 23990081-XX

1.2 Adult Anterior Paddles 24990082-01 450 AA

1.3 Adult Anterior-Posterior Paddles 24990113-01 450 APA

1.4 Adult Anterior Paddles 24990114-03 450 AI

1.5 Pediatric Anterior Paddles 24990082-02 450 PA

1.6 Pediatric Internal Paddles 24990114-02 450 PI

1.7 Infant Internal Paddles 24990114-01 450 II

1.8 Adult Anterior Paddles with Remote Charge 24990082-03 450 AAR

1.9 Patient Cable Assy. 3 Electrode -21 D24990118-01

1.10 Tube XXXXXX (712) 1042507001

1.11 D320/400 Shipping List

1.12 D320/400 Operators Manual

1.13 D320/400 Maintenance Manual

2.0 OVERALL DESCRIPTION

The D320/400 (Ref. 1.1) is a portable defibrillator with integral isolated input, solid trace, ECG monitor scope. The D320/400W contains in addition a 40 mm strip chart recorder. They may be used for non-synchronous ventricular defibrillation or synchronous conversion of arrhythmias. Power is derived from internal rechargeable batteries or from the AC power line whenever the unit is connected to the AC power line via the internal charger.

Standard accessories included in the D320 Shipping List (Ref. 1.11) are:

1 - Adult Anterior Paddle Set (Ref. 1.2)
1 - Patient Cable-21(Ref. 1.8)
1 - Tube XXXXXX Electrode Paste (Ref. 1.9)
1 - Operator's Manual (Ref. 1.11)
1 - Shipping Carton

Optional Accessories are alternate paddles described in section 4.

3.0 CONFIGURATIONS

23990081-01 Battery Operated Defibrillator - D320 (120V)
23990081-02 Battery Operated Defibrillator - D320 (220V)
23990081-03 Battery Operated Defibrillator with Writer - D320W (120V)
23990081-04 Battery Operated Defibrillator with Writer - D320W (220V)
2399 Battery Operated Defibrillator - D400 (120V)
2399 Battery Operated Defibrillator - D400 (220V)
2399 Battery Operated Defibrillator with Writer - D400 (120V)
2399 Battery Operated Defibrillator with Writer - D400W (220V)

4.0 FUNCTIONAL CHARACTERISTICS

4.1 DEFIBRILLATOR FUNCTIONAL CHARACTERISTICS

The defibrillator becomes operational in the non-synchronous mode when the power switch is turned ON and the paddle connector is attached. A charge cycle is initiated by depressing and holding the MANUAL CHARGE button until the desired charge is reached. Automatic charge to 160 (200) or 320 (400) joules is accomplished by depressing the AUTO CHARGE 160 (200) or AUTO CHARGE 320 (400) buttons respectively. An audible tone and a DELIVERED ENERGY bar display on the scope indicate when a charge is in process. When the charge cycle is complete, the audible tone stops and the DELIVERED ENERGY meter indicates the amount of energy to be delivered. The stored energy is delivered in the form of an Edmark waveform by pressing the buttons located on the anterior paddles or, if interior paddles are used, pressing the INTERNAL PADDLE switch located on the control panel.

For safety and equipment protection, a charge cycle is followed by an automatic time out that dumps the stored energy (disarms) after 45 seconds if energy is not delivered or the charge button pressed again within the time out period. The stored energy is also automatically dumped when the power switch is turned OFF. The operator may disarm the unit by depressing the DISARM button.

4.1.1 Delivered Energy Indicator

The DELIVERED ENERGY INDICATOR displays the energy to be delivered into a 50 ohm load as a horizontal line at the top of the CRT screen. When a charge is initiated, the end of a solid bar will follow the amount of energy to be delivered.

4.1.2 Paddle and Accessory Storage

A molded paddle holder is in the defibrillator front panel cover for one set of anterior-anterior adult defibrillator paddles. One (D320W/400W) or two (D320/400) accessory holders are located below the front panel to hold cables, electrodes, and paste. Under normal usage, the defibrillator is stored or transported with defibrillator cables connected. This approach minimizes the number of steps needed to bring the defibrillator from an idle state to the emergency non-synchronous mode.

4.1.3 Anterior-Anterior paddles

Anterior-anterior paddle assemblies are available with two electrode sizes: adult 8.5 cm (Ref. 1.2) and pediatric 5.0 cm (Ref. 1.7). Each assembly consists of a

connector, two paddles with discharge buttons, and a dual coiled cord extendable to 10 feet.

Ethylene oxide sterilization is the only permissible sterilization technique for all of these paddles.

4.1.4 Anterior-Anterior Paddles with Remote Charge (Optional)

Same as 4.1.3 except one paddle will have a charge button that functions identically to MANUAL CHARGE button on the front panel (Ref. 1.8).

4.1.5 Anterior-Posterior Paddles

An anterior-posterior paddle assembly (Ref. 1.4) is available for use only on adults. It consists of an anterior paddle identical to the 8.5 cm paddle in a 4.1.3, a posterior 12 cm paddle, a dual 10ft. coiled cord, and connector.

4.1.6 Internal Paddles

Internal paddle assemblies are available with three electrode sizes: adult 8.5 cm (Ref. 1.4), pediatric 5.0 cm (Ref. 1.5), and infant 2.5 cm (Ref. 1.6). Each assembly consists of a connector, 2 paddles, and a dual coiled cord extendable to 10 ft.

4.2 ECG AMPLIFIER AND SOLID TRACE SCOPE FUNCTIONAL CHARACTERISTICS

4.2.1 ECG Amplifier

The ECG amplifier is an isolated, variable gain amplifier which feeds the display, QRS detector, and output jack. Input to the amplifier is through the defibrillator paddle connector or through the patient cable. A lead selector switch selects the paddles, or leads I, II, or III for input. The amplifier incorporates the following features:

1. **Slew Rate Limit - Limits the slew rate and, therefore, the amplitude of the pacer pulses so that they can be seen on the display and will not trigger the QRS detector in most lead configurations.**

2. **Fast Recovery Circuit - Returns the signal to on screen limits within 0.5 seconds after defibrillation or other overload.**

4.2.2 Solid Trace Display

The solid trace display shows the last 4 seconds of ECG waveform on the screen. The waveform appears as if a strip chart recorder were writing the ECG at the right hand edge of the screen and the paper was being pulled from right to left. Current information is displayed at the right of the screen with information becoming increasingly older towards the left. When operating the defibrillator in the synchronous mode, sync pulses appear showing where the energy would have been delivered had the discharge buttons been pushed. The waveform may be stopped or "frozen" for review by pushing the latching FREEZE button.

4.3 HEART RATE METER FUNCTIONAL CHARACTERISTICS

The heart rate meter displays heart rate as a bar at the screen bottom. The heart rate is also compared to alarm limits that are displayed on the same bar. When a limit is exceeded for longer than three seconds, the red alarm led blinks, an audible alarm sounds, and the hard copy writer runs (D320W/400W only). Alarms are disabled or reset by putting the LOW LIMIT knob fully counter-clockwise and the HIGH LIMIT fully clockwise. In this position the limit indications are not displayed on the screen.

The threshold for QRS detection is automatically adjusted depending on the amplitude of the QRS complex. The minimum threshold is equivalent to 0.6 cm on the scope display. At maximum gain, a 0.3 mv QRS complex will be detected. Detection of a complex will cause an audible beep if the BEEP push-button is depressed. Proper adjustment of the gain control will result in an R-wave amplitude on the screen of one to two cm.

*4.4 SYNCHRONIZED CARDIOVERTER FUNCTIONAL CHARACTERISTICS

The synchronizer detects the peak of the R wave and, after the discharge buttons on both defibrillator paddles have been pushed, delivers the stored energy. The QRS amplitude must be set to at least 0.6 cm on the scope display using the SIZE control. QRS detection is verified by an audible QRS beep and by a SYNC pulse displayed on the scope at the time relative to each QRS complex that the energy would have been delivered.

4.5 WRITER FUNCTIONAL CHARACTERISTICS (D320W/400W only)

The D320/400W is equipped with a 40 mm direct hard copy writer. The writer is started manually by the RECORD push-button on the front panel or automatically on alarm. No other controls are provided. Gain of the writer is equal to the gain of the scope. Therefore, setting the QRS size control to a convenient point for the scope will produce a reasonable gain for the writer. Centering of the writer is automatic to within approximately .25 cm. An internal stylus heat adjustment is provided. An external control is not needed due to the regulation of the stylus power supply.

4.6 MODES OF OPERATION

The defibrillator has two modes of operation: non-synchronous defibrillation and synchronous defibrillation. The defibrillator is always in the non-synchronous defibrillation mode when power is turned on. It can be switched from the non-synchronous mode to the synchronous mode by pressing the SYNC ON push-button. It can be returned to the non-synchronous mode by pressing the SYNC OFF push-button. Synchronous mode is indicated by a SYNC light on the front panel and by sync pulses appearing on the scope coincident with QRS detection.

*4.7 OPERATOR CONTROLS

4.7.1 ON/OFF

A two push-button switch turns on the ECG amplifier and Solid TraceScope and puts the unit in the non-synchronous mode when ON is depressed.

When OFF is depressed it dumps (disarms) the defibrillator capacitor and switches off all power to the unit. Closing the front cover automatically depresses OFF.

4.7.2 MANUAL CHARGE

A momentary push-button that causes the capacitor to be charged while depressed.

4.7.3 AUTO CHARGE 160 (AUTO CHARGE 200)

A momentary push-button which initiates an automatic charge to 160 joules delivered.

4.7.4 AUTO CHARGE 320 (AUTO CHARGE 400)

A momentary push-button which initiates an automatic charge to 320 joules delivered.

4.7.5 PADDLE CHARGE (Optional)

A momentary push-button located on the right paddle which functions identically to the MANUAL CHARGE push-button.

4.7.6 SYNC ON/SYNC OFF (Labeled SYNC/DEFIB ON D400/400W)

Two momentary push-buttons used to select synchronous or non-synchronous mode of operation. Pressing SYNC ON after the power is turned on puts the unit in the synchronous mode and illuminates the SYNC light. The unit is put in the non-synchronous mode when power is turned on or by pressing SYNC OFF when operating in the synchronous mode.

4.7.7 DISARM

A momentary push-button that is used to dump the internal stored charge. It is used if a lower energy than the one already selected is desired, or if no more countershocks are to be delivered.

4.7.8 QRS SIZE

A potentiometer used for setting the gain of the ECG amplifier. Gain may be varied from X300 at fully CCW to X3000 at fully CW. At center position, the gain is X1000.

4.7.9 FREEZE

A latching push-button that causes the scope to cease updating.

4.7.10 1MV

A momentary push-button that injects a 1 mv +/- 2.5% signal.

4.7.11 BEEP

A latching push-button that activates the QRS beep when depressed.

4.7.12 HIGH LIMIT

A potentiometer used for setting the alarm high rate limit over a range of at least 100 to 250 BPM. It is set to 120 BPM with knob pointer is straight up.

4.7.13 LOW LIMIT

A potentiometer used for setting the alarm low rate limit over a range of at least 0 to 150 BPM. It is set to 60 BPM with knob pointer is straight up.

4.7.14 RECORD

A latching push-button that starts the writer when depressed. The writer is always started on alarm.

4.7.15 LEAD SELECT

Four interlocking push-buttons labeled PADDLES, I, II, III that select paddles or standard leads I, II, III respectively as input to the ECG amplifier. A three-lead cable with RA, LA, and LL (which may be labeled R) can be used.

*4.8 INDICATORS

4.8.1 BATTERY LOW

A red lamp that begins flashing when the battery has a minimum of ½ hour of continuous monitoring capacity left or 2 charges to 320 joules (1 charge to 400 joules). The lamp flashes to indicate circuit operation when power is turned on.

4.8.2 SYNC

An amber LED that illuminates when the unit is operating in the synchronous mode.

4.8.3 DELIVERED ENERGY, JOULES

An illuminated bar that indicates the energy in joules to be delivered into a 50 ohm load.

4.8.4 TEST

A light located on the defibrillator paddle holder that illuminates when a counter shock of at least 300 joules is discharged into the paddle holders.

4.8.5 ALARM

A red light that flashes during an alarm.

4.8.6 LINE

Two red lights that illuminate when AC power is being received by the unit.

4.8.7 QRS Beep

An audible tone that is produced every time a QRS complex is detected when the BEEP push-button is depressed.

4.8.8 Charging

A audible tone that increases in pitch as the capacitor charges.

4.8.9 Sync Pulse

A negative pulse displayed on the ECG trace with its center within 20 ms of where the energy should have been delivered if the DISCHARGE BUTTON(S) had been pushed.

4.8.10 Heart Rate Bar

An illuminated bar graph showing Heart Rate and alarm limit settings.

*4.9 CONNECTORS

4.9.1 Defibrillator Paddle Connector

G pin High Voltage Connector

Pin D -High Voltage Paddle Lead
Pin A +High Voltage Paddle Lead
Pin F Ground
Pin C INTPDL - (Internal Paddle Jumper)
Pin B FDLSW - (Paddle Switch)
Pin E RMTCHG - (Remote Charge Switch)

4.9.2 Isolated Input Connector

5 pins MS series Connector - Located on front panel.

Pin A Right Arm
Pin B Left Arm
Pin C Left Leg
Pin D Left Leg
Pin E Left Leg

4.9.3 ECG/Output Connector

3-wire phone jack on front panel
Tip - ECG Output
Ring - Signal Ground
Sleeve - Chassis Ground

5.0 PERFORMANCE CHARACTERISTICS

5.1 DEFIBRILLATOR OUTPUT

5.1.1 Waveform: Monophasic pulse (Edmark Waveform)

***5.1.2 Energy Range: 10-320 joules delivered into a 50 ohm load.**
D320/320W

	Energy Range: D400/400W	**10-400 joules delivered into a 50 ohm load.**
***5.1.3**	**Energy Accuracy: DELIVERED ENERGY INDICATOR OR AUTO 320 (400) and AUTO 160 (200) push-buttons**	**Error less than 10% or 4 joules, whichever is greater, into 50 ohms and 25% or 4 joules, whichever is greater, into a 25 to 100 ohm load when measured in accordance with XXX recommendations.**
5.1.4	**Pulse Width:**	**95% of the energy delivered in <5 ms into 50 ohm load.**
***5.1.5**	**Charge Time: (D320/320W)**	**Charges to 320 joules in 10 sec. max. 8.5 sec. typical.**
	Charge Time: (D400/400W)	**Charge to 400 joules in 12 sec. max. 10.5 sec. typical.**
5.1.6	**Pulse Rate: <5**	**Deliver 15 400-joule counter shocks in minutes.**
5.1.7	**Energy Loss Rate:**	**<15% in 30 seconds.**
5.1.8	**Charge Dump Time**	**<25 volts left in 4 seconds and <2 joules in 3 minutes after activation of capacitor dump circuit.**
***5.1.9**	**Isolation**	**Withstands 8 KV DC from either paddle to chassis with relay in fire position.**

5.2 ECG AMPLIFIER

***Frequency Response:**	**.5 to 40 Hz. +0, -3 db max. from isolated input connector to ECG output on front connector or scope display at 1 cm scope deflection.**
***Risk Current:**	**<10 ua at 120 v 60 Hz without patient cable. <20 ua with 120 VAC applied to electrode end of ECG patient cable.**
*** Gain:**	**adjustable x300 to x3000. x1000 at nominal gain position.**
Input Impedance:	**>1 megohm differential, DC to 60 Hz through patient cable.**
Input Offset Tolerance:	**>1 volt**
Input Dynamic Range:	**+/- 3.5 mv at nominal gain setting.**

***Isolation Voltage:**	**2500 volts RMS at 60 Hz from any patient lead or combination of patient leads to AC line for one minute.**
Defibrillator Protection:	**Will withstand 5 pulses at 20 second intervals from defibrillator set to 400 ws delivered energy and delivered across a 100 ohm load in parallel with any two patient cable leads.**
***Reset Recovery**	**Automatic return to on screen within .5 seconds after an electrosurgical or defibrillator overload.**
Slew Rate:	**Internally limited at .2 to .25 mv/ms referred to input at nominal gain.**
***Calibration Signal:**	**1 mv +/-2.5% referred to input.**
Output:	**High-level single-ended output on front panel. Output level dependent on gain setting.**
Output Impedance:	**<100 ohms**
Output Dynamic Range:	**3.5 volts +/-10%**
***Output Offset**	**<50 mv for DC input @ 25°C <200 mv @ nom gain over full temp range**
Output Current	**>+/-5 ma**
***Noise:**	**<5 uv RMS referred to input at ECG output with RA and LA connected to RL by shielded 25 Kohm resistors. <50 uv RMS referred to input at scope display at nominal Gain setting.**
Common Mode Input Impedance:	**>12 megohms from patient leads to chassis ground, from DC to 50 Hz.**

5.3 SOLID TRACE SCOPE

Viewing Area:	**3.94" wide x 3.15 high (8x10 cm)**
***Gain**	**.33 mv/cm to 3.3 mv/cm from patient leads to scope display depending on ECG amplifier gain setting.**

Brightness:	**Internal adjustment.**
Sweep Speed:	**25 mm/sec. +/-5%**
Warm-up:	**Visible in 15 seconds.**
Memory Time:	**4 seconds visible**
Sample Rate:	**240/sec.**
Resolution:	**8 bits**
Phosphor:	**P31**
Refresh Rate:	**60 Hz**
***Transient Response:**	**<5 percent overshoot to step input of any magnitude up to full scale.**
***Frequency Response:**	**.5 to 40Hz +0-3db max. from isolated input to scope display @ 1 cm deflection.**
Horizontal Sweep Linearity:	**Better than 5% over full viewing area.**
Vertical Linearity:	**Better than 5% over 6 cm central viewing area from isolated input to scope display.**
Drift:	**Baseline will not drift more than .5 cm with 5 minutes after power turn on.**
Sampling Noise:	**<.3 mm at any gain setting.**

5.4 SYNCHRONIZED CARDIOVERTER

QRS Detector:	**Automatic threshold greater than .6 cm either polarity QRS complex.**
***Sensitivity:**	**<.3 mv at maximum gain setting**
Range:	**0-250 beats per minute.**
QRS Tone:	**1 KHz tone**
Marker Pulse:	**Shown on scope +/-20 ms from beginning of counter shock.**
***Discharge Delay:**	**Energy is delivered within 40 ms of the R wave peak with proper gain setting.**

5.5 HEART RATE METER

***Range**	**0-250 BPM**

***Accuracy**	**3 BPM or 5% of reading whichever is greater.**
Response Time:	**<5 seconds for rates greater than 50 and an input step change of 70 BPM**
Alarm Setting Accuracy:	**Better than +/-5 BPM**
Alarm Delay:	**3 Seconds +/-1 second**
***Pacer Artifact Rejection:**	**Will not respond to pacer spikes <= 4 ms with proper lead placement.**

5.6 WRITER (D320W/400W only)

Linearity:	**1% of full scale**
***Frequency Response:**	**.5 to 40 Hz +0, -3db maximum from isolated input connector at 1 cm deflection.**
Chart Width:	**40 mm**
Chart Speed:	**25 mm/sec +/-3%**

5.7 DEFIBRILLATOR BATTERY SUPPLY

***Battery Life:**	**Minimum of 5 hours of monitoring, 1.7 hr (D320/320W) of monitoring with writer running, or 50 defibrillator charges at 320 joules, or any proportional combination at 25°C. 6 hours of monitoring or 60 shots typical.**
***Battery Life (D400/400W)**	**Minimum of 5 hours of monitoring, 1.7 hrs of monitoring with writer running, or 40 defibrillator charges at 400 joules or any proportional combination at 25°C. 6 hours of monitoring or 50 shots typical.** **Battery Type: NiCad 12 volt battery pack located inside unit.**
***Battery Charge Time:**	**14 hours to full charge**
***Low Battery Indicator:**	**Comes on when minimum of 1/2 hour of monitoring or 2 charges to 320 joules of battery capacity left.**

5.8 AC LINE REQUIREMENTS

Input Requirements	**97/127 VAC 48-65 Hz. -01,-03,-05, -07 194/254 VAC 48-65 Hz. -02, -04,-06,-08**
Power Requirements:	**55 watts max, with fully discharged battery in charge mode.**
***Green Wire Leakage:**	**<50 ua RMS at 120 VAC 60 Hz measured with AAMI load.**
***Hipot:**	**2500 VAC RMS 60 Hz between AC hot and neutral and green wire ground.**

5.9 PADDLES

Electrode Finish:	**<250 micro inches RMS surface roughness.**
Electrode Material	**400 series stainless steel.**
Handle Material:	**Flame resistant plastic**

5.10 PHYSICAL CHARACTERISTICS

5.10.1 Size: 17.81" x 15.10" x 8.94"
45.24 cm x 38.35 cm x 22.54 cm

Weight: 33 lbs. (-01,-03,-05,-07)
37 lbs. (-02,-04,-06,-08)

5.11 ENVIRONMENTAL CHARACTERISTICS

5.11.1 Temperature

Operating: **-10°C to 55°C (14°F to 131°F)**

Storage: **-25°C to 55°C (-13°F to 158°F)**

Notes: **Continuous battery charge over 40°C ambient reduces battery life. Long term storage over 50°C reduces battery life.**

5.11.2 Humidity

Operating: **5% to 96% relative humidity**

Storage: **5% to 80% relative humidity**

5.11.3 Atmospheric Pressure

70 kPA to 103 kPA

5.11.4 Shock and Vibration

Shall comply with the shock and vibration requirements of section 3.2.3 of the XXX Cardiac Defibrillator Standard, document number XXX-XXX-021-0001.

TITLE: IN4278 ZENER DIODE SPECIFICATION NUMBER

Drafted by _____ App. _____ Date _____

REV.	ECN History Notes	Date

1. SCOPE: This specification describes a one-watt zener diode used for voltage reference in the XYZ Stimulator.

2. ELECTRONIC CHARACTERISTICS

2.1 Zener Voltage: 3.1 vdc @ 76 madc

2.2 Maximum Zener Impedance: 10 ohms @ 76 madc

2.3 Reverse Leakage Current: (25%) 100 microamps (max) @ l vdc

3. TESTING: All diodes shall meet the requirements of JANTX IN4278 as specified in MIL-S-19500/127G.

4. PHYSICAL CHARACTERISTICS

4.1 Diodes shall be packaged in a void-free silicone case.

4.2 Leads shall be readily solderable.

5. MARKING

5.1 The cathode shall be identified by a color band.

5.2 An identification number and lot number or date code shall represent a specific manufacturing period.

5.3 All markings shall be permanent such that cleaning solutions will not remove the markings.

6. CERTIFICATION

6.1 A certification of compliance with this specification and a test data sheet must accompany each lot shipped.

6.2 Certification must include a statement that no changes have been made in materials or physical or electrical characteristics.

7. APPROVED SUPPLIERS

7.1 XXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXX

OPEN HERE

HAND-SWITCHING PENCIL
STERILE REUSABLE
Catalog No. E2502B

STERILITY GUARANTEED UNLESS PACKAGE HAS BEEN DAMAGED OR OPENED:

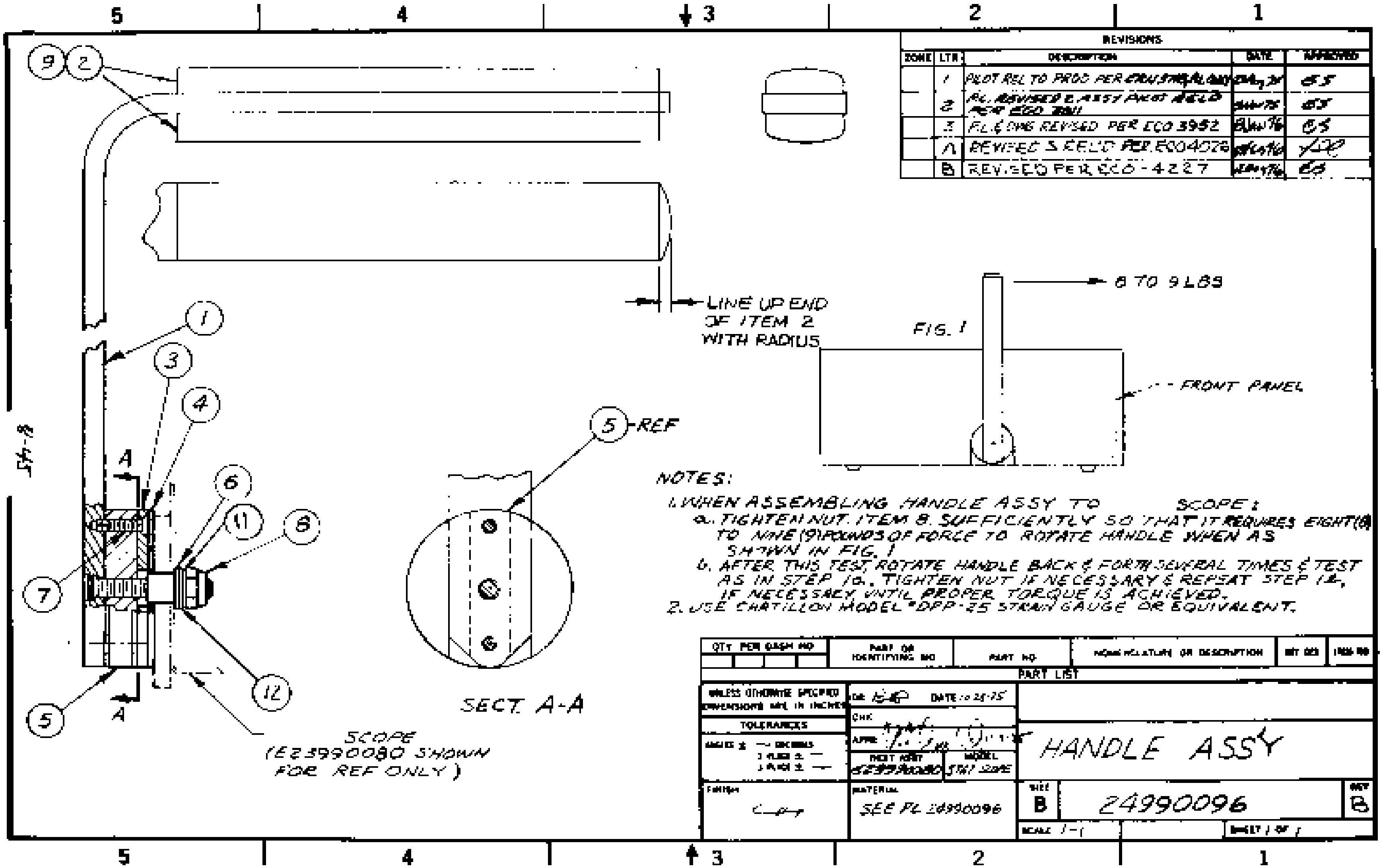
CONTENTS:
One sterile reusable Hand-switching Pencil with 10 follt cord and plug and disposable blade electrode. Accepts all standard 3/32" shaft electrodes.

DIRECTIONS:

1) Open package by peeling apart at arrow.
2) Remove LectroSwitch®Pencil from sterile package using aseptic technique. Do not perrmit LectroSwitch®Pencil to contact unsterile end of package or any object outside the sterile field.
3) Check blade electrode connection for secure fit prior to use
4) Insert plug connection into active hand-switching receptacle on generator. An adapter may be required for generators not manufactured by Valleylab, Inc.
5) Remove protective sleeve from blade electrode.

CAUTION: AFTER USE THE LECTROSWITCH®PENCIL MUST BE STERILIZED. DISCARD THE DISPOSABLE BLADE ELECTRODE BEFORE REPROCESSING. RECOMMENDED STERILIZATION TECHNIQUE IS SHOWN ON PACKAGE INSERT IN BOX CONTAINING LECTROSWITCH®PENCILS.

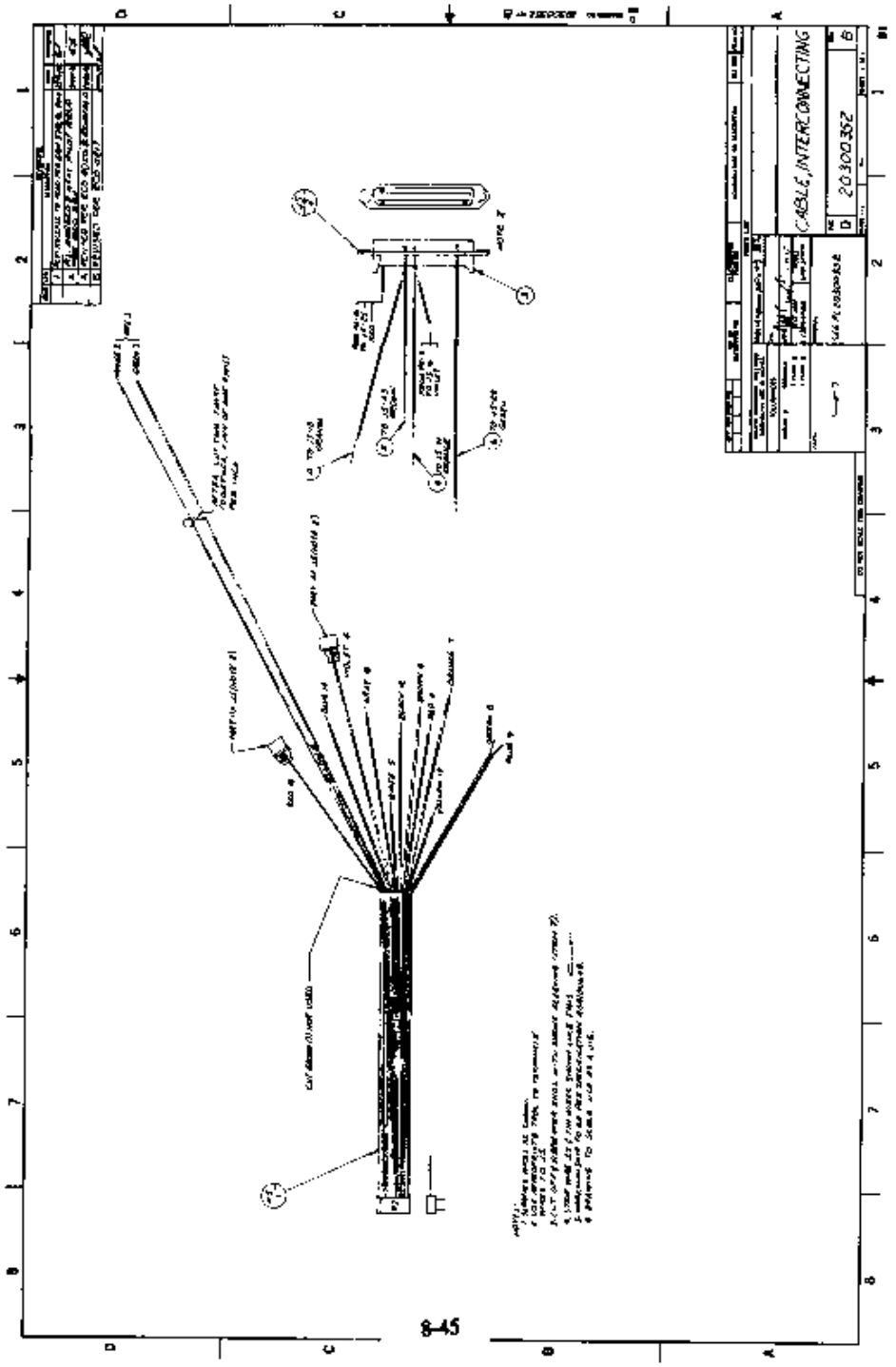
NOTE: GOOD OPEATING ROOM PRACTICE SUGGESTS THAT ACTIVE ACCESSORIES BE PLACED AWAY FROM THE PATIENT WHEN NOT IN USE.


REVISIONS
ZONE | LTR | DESCRIPTION | DATE | APPROVED
1 PILOT REL TO PROD PER
2 P.L. REVISED & ASSY
3 P.L. & DWG REVISED PER ECO 3952
A REVISED & REL'D PER ECO 4026
B REVISED PER ECO - 4227
8 TO 9 LBS
LINE UP END OF ITEM 2 WITH RADIUS
FIG. 1
FRONT PANEL
5 -REF
NOTES:
1. WHEN ASSEMBLING HANDLE ASSY TO SCOPE:
a. TIGHTEN NUT, ITEM 8, SUFFICIENTLY SO THAT IT REQUIRES EIGHT (8) TO NINE (9) POUNDS OF FORCE TO ROTATE HANDLE WHEN AS SHOWN IN FIG. 1
b. AFTER THIS TEST ROTATE HANDLE BACK & FORTH SEVERAL TIMES & TEST AS IN STEP 1a. TIGHTEN NUT IF NECESSARY & REPEAT STEP 1a, IF NECESSARY, UNTIL PROPER TORQUE IS ACHIEVED.
2. USE CHATILLON MODEL #DPP-25 STRAIN GAUGE OR EQUIVALENT.
SECT. A-A
SCOPE (E23990080 SHOWN FOR REF ONLY)
PART LIST
UNLESS OTHERWISE SPECIFIED DIMENSIONS ARE IN INCHES
TOLERANCES
MATERIAL
SEE PL 24990096
HANDLE ASSY
SIZE B
24990096
REV B
SCALE 1-1
SHEET 1 OF 1
8-45

COMPANY LOGO	PARTS LIST	PL	24990672	REV C
USED ON 29330080	TITLE Handle Assemby			SHEET 1 OF 1
DRAWN DATE	CHECKED DATE		APPROVED DATE	

ITEM NO.	SIZE	PART NO.	DESCRIPTION	REF.DES.	QTY.PER.TAB NO.	
					.01	.02
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						

NOTES:


CABLE, INTERCONNECTING
2030352
8-45

COMPANY LOGO	PARTS LIST	PL	20500681	REV B
USED ON Port Scope	TITLE Cable Interconnecting & Point to Point Wiring			SHEET 1 OF 1
DRAWN DATE	CHECKED DATE	APPROVEDDATE		

ITEM NO.	SIZE	PART NO.	DESCRIPTION	REF.DES.	QTY.PER.TAB NO.	
					.01	.02
1						
2						
3						
4						
5						
6						
7						

Notes:

1.0 PRODUCT DESCRIPTION

1.0 Number XXXXXXX, Product specification

2.0 PREPARATION Manufacturing

2.1 Purchase Specifications

2.101	**PS 01-0003**	**XXXXXXX Starch**
2.102	**PS 01-0008**	**Sodium Hydroxide**
2.103	**PS 01-0017**	**Hydrochloric XXXXXXXXXXX**
2.104	**PS 01-0002**	**XXXXXXXXXXXXXXXXXXXXXXXX**
2.105	**PS 01-0005**	**XXXXXXXXXXXXXXXXXXXXXXXX**
2.106	**PS 01-0012**	**XXXXXXXXXXXXXXXXXXXXXXXX**
2.107	**PS 01-0004**	**Sodium Chloride**
2.108	**PS 01-0007**	**XXXXXXXXXXXXXXXXXXXXXXXX**
2.109	**PS 01-0001**	**XXXXXXXXXXXXXXXXXXXXXXXX**

2.2 Preparation

2.201	**#1076**	**Starch pretreatment**
2.202	**#1079,1080**	**XXXXXX Diluent solution**
2.203	**#1078 XXXX**	**Iodine solution**
2.204	**#1082 XXXX**	**Substrate**

3.0 FILLING, LABELING AND PACKAGING

3.1 Purchase Specifications

3.101	**PS 02-0201**	**Tube**
3.102	**PS 02-0103**	**Cap**

Cat. XXXXXXX

3.103	**PS 02-0001**	**Bottle**
3.104	**PS 02-0101**	**Cap**
3.105	**PS 05-0006**	**Teflon liner**
3.106	**PS 02-0701A**	**Label**
3.107	**PS 03-0701**	**Instruction sheet**
3.108	**PS 03-0320**	**Platforms**
3.109	**PS 03-0001**	**Boxes**

TITLE: DEVICE MASTER RECORD FOR AMAYLASE			
Dr By:	**Date**	**Dwg No:**	**Sheet 1 of 2**
App'd:	**Date:**	**Revision A**	**Date**
ECN			

Cat. XXXXXXX

3.110	**PS 02-0002**	**Bottle**
3.111	**PS 02-0102**	**Cap**
3.112	**PS 05-0007**	**Teflon liner**
3.113	**PS 02-0701B**	**Label**
3.114	**PS 03-0707**	**Instruction sheet**
3.115	**PS 03-0301**	**Boxes**
3.116	**PS 03-0002**	**Platforms**

3.2 XXXXXXX Production

3.201	**SOP-XXXXX**	**Filling, labeling and packaging**

4. Quality Control Specifications

4.1 Raw Material Specification (RM)

4.101	**RM 01-0002**	**XXXXXXXXXXXXXXXXXXXXXX**
4.102	**RM 01-0003**	**XXXXXXXXXXXXXXXXXXXXXX**
4.103	**RM 01-0005**	**XXXXXXXXXXXXXXXXXXXXXX**
4.104	**RM 01-0007**	**XXXXXXXXXXXXXXXXXXXXXX**
4.105	**RM 01-0008**	**Sodium Hydroxide**
4.106	**RM 01-0012**	**XXXXXXXXXXXXXXXXXXXXXX**
4.107	**RM 01-0017**	**Hydrochloric XXXXXXXXXX**
4.108	**RM 01-0004**	**Sodium Chloride**
4.109	**RM 01-0001**	**Bottle (3200-01)**
4.110	**RM 01-0002**	**Bottle (3200-10)**
4.111	**RM 01-0101**	**Cap (3200-01)**
4.112	**RM 01-0102**	**Cap (3200-10)**
4.113	**RM 02-0701A**	**Label (3200-01)**
4.114	**RM 02-0701B**	**Label (3200-10)**
4.115	**RM 03-0001**	**Boxes (3200-01)**
4.116	**RM 03-0002**	**Platform (3200-10)**
4.117	**RM 03-0301**	**Boxes (3200-01)**
4.118	**RM 03-0320**	**Boxes (3200-10)**
4.119	**RM 03-0701**	**Instruction sheet (3200-01)**
4.120	**RM 03-0707**	**Instruction sheet (3200-10)**
4.121	**RM 05-0006**	**Teflon liner (3200-01)**
4.122	**RM 05-0007**	**Teflon liner (3200-10)**
4.123	**RM 01-0001**	**XXXXXXXXXXXXXXXXXXXXXX**

4.2 In-process Specifications

4.201	**SOP-58200B-0**	**0ptical Density of XXXXXXX substrate**

4.3 Final specifications

4.301	**QC-PB-007**	**Finished goods quality control-XXXXXXX set**

5. Final Release

5.1 Final Release Specification

5.101	**#1087**	**Final Product Release Form**

Device Master Record For Amaylase	**Dwg No**	**Sheet 2 Of 2**

1. PRODUCT SPECIFICATION FOR AMYLASE, CATALOG NO. 3200

1.1 Product name: Amylase Set

1.2 Description of product

This Amylase Set is used for the quantitative determination of amylase in biological fluids.

The principle of the procedure is as follows:

Starch + H_20 amylase > colorless starch fragments

Unhydrolyzed Starch + I_2 ----> colored starch-iodine complex

The color produced by the starch-iodine complex after 7.5 minutes incubation of substrate with specimen and 15 minutes color development is compared with a reagent blank. The decrease in absorbanceoptical density (OD) at 660 nm is proportional to amylase activity in the specimen because the enzyme hydrolyzes starch to fragments that do not react with the iodine reagent.

1.3 Product availability

Catalog No.: 3200-01
Catalog No.: 3200-10

1.4 Components of product

Catalog No. 3200-01
15 Tubes of lyophilized substrate
1 Bottle (10 ml) Iodine (.OIN)
1 Instruction sheet

Catalog No. 3200-10
100 tubes lyophilized substrate
2 Bottles (30 ml ea.) Iodine (.OIN)
1 Instruction sheet

1.5 Storage of reagent

Store at room temperature. Do not refrigerate.
Minimum shelf life is one year.
Do not use any substrate tube in which moisture is observed.

1.6 Stability of specimen

Amylase activity in serum is stable up to one week at room temperature and for one to two months if refrigerated at 2 to 8°C.

1.7 Procedure for urine amylase

Collect a timed (minimum of 2 hours) sample of urine and measure the volume. Follow the same procedure as used for serum amylase. Calculate the amylase activity excreted in the urine per hour as follows:

Urine amylase (unit/hour) =

$$= \frac{\text{OD Reagent blank - OD Specimen}}{\text{OD Reagent blank}} \times \text{IOV/H} \times \text{Tf}$$

V = total volume of timed urine specimen in milliliters;
H = total collection time in hours;
Tf = temperature correction factor.

Example:

2 hour volume of urine = 130 ml;
OD blank= 0.57;
OD Specimen = 0.48;
Temperature = 37°C;

Urine amylase (unit/hour) =

$$= \frac{0.57 - 0.48}{0.572} \times \frac{10 \times 130}{2} \times 1 = 103$$

Caution: Some urine specimens may contain reducing substances which could exhaust the iodine reagent.

1.8 Units

One amylase unit is defined as that amount of enzyme activity which, under the conditions of this procedure, will hydrolyze 10 mg of starch in 30 minutes to a stage at which no color is generated with iodine.

1.9 Normal Range

Normal range for serum is 50 to 200 units at 37°C. Infants below two months have no measurable serum amylase. Adult level is reached by the age of one year. The above normal range includes an average serum blank of 25 amylase units. Normal values for urine is less than 375 units per hour at 37°C.

1.10 Precision

Coefficient of variation of 5 to 6 percent at a level of 120 units and 3 to 5 percent at a level of 250 units are obtained with good laboratory technique.

1.11 Performance characteristics

This assay measures amylase levels up to 500 units per 100ml specimen in a linear manner. Specimens with higher activity must be diluted by the procedure given in Note 2 [not reprinted in this manual]. The calculated value includes a serum blank, which averages about 25 units in human sera. Control sera may have larger serum blanks, often up to 100 units. Values obtained on patient sera when corrected for the serum blank activity of approximately 25 units are very close to the values obtained by the Somogyi Saccharogenic method.

1.12 Cautions

This product must be protected from contamination by amylase. Saliva is a very potent source of amylase. Perspiration contains some amylase as do other body fluids. Insensible droplets of saliva are projected during speech, sneezing, etc.

Face masks and hair covering must be worn during solution and diluent preparation, solution filling, tube racking and capping, and when handling any raw material defined for use with this diagnostic test.

Equipment used in the procedure should be designed "For Amylase Only". Glassware and other equipment suspected of amylase contamination must be rinsed with XXXXXXX. Avoid contamination with detergents or soap. (See SOP #G021). Observe safety precautions when handling acids (SOP #G022).

1.13 Manufacturing Flow Sheet.

See Form No. 9926. [Not reprinted in this Manual].

FOR USE IN CATALOG Numbers: XXXX-01 15 tests and XXXX-10 100 tests

Batch No. _____ Code No. _____ Date _____

Prepared by _____ Checked by _____

MASKS MUST BE WORN THROUGHOUT THIS PROCEDURE TO PREVENT SALIVA CONTAMINATION.

FOR 50 LITERS OF AMYLASE DILUENT SOLUTION:

1. **Weigh the following chemicals and place them in 43 liters of deionized water in a calibrated clean container.**

DEIONIZED WATER: Source _____ Vol. _____ ml Done By _____
Conductivity Light: On _____ Off _____ Checked By _____

RM. NO.	CHEMICAL	VENDER CODE	LOT NO.	AMOUNT REQ'D	WEIGHT	WEIGHED BY	BY
01-0004	Sodium Chloride	_____	____	425.0 g ±0.1	G ____ T ____ N ____	_____	_____
01-000X	XXXXXX Basic	_____ _____	____ ____	523.25 ±0.1	G ____ T ____ N ____	_____ _____	_____ _____
01-000X	XXXXXX Basic	_____	____	1275.0 g ±0.1	G ____ T ____ N ____	_____	_____

Note: Slowly add the sodium XXXXXXXX to prevent caking.

Procedure Amylase Diluent Solution No. _____ Rev. _____
Completed by _____ Date _____ Date Eff. _____
Checked by _____ Date _____ App'd _____

2. Stir the diluent until all of the salts go into solution.

Done by _____

3. Check the pH of the solution against 7.00 pH reference buffer.

Initial pH _____ Checked by _____

4. Adjust the solution to a pH of 7.00 + 0.05 @ 25°C using 2N NaOH
mls of _____ used. Lot No. _____ pH ___ @ 25°C

Checked by _____

5. Add 125 mls of 1% XXXXXX solution & mix well. Done by _____

No. of mls added _____. Supplier_____ Lot No. _____

6. Bring the volume to 50 liters with deionized water and mix well. Re-check the pH. It should still be 7.00 + 0.05 @ 25°. Adjust, if necessary, with 2N NaOH or 6N HCl.

DEIONIZED WATER:

Source _____ Final Vol. _____ mls. Done by _____

Conductivity Light: On _____ Off _____ Checked by _____

mls of _____ used to adjust. Lot No. ____ Done by _____

Final pH @ 25°C_____ Checked by _____

7. Solution must be approved by the Solutions Supervisor(s) or their designee before it can be used. Approved by: _____ Date _____

8. The Solution is now ready to be used in the preparation of Amylase.
It will be filtered as it is during that preparation.

9. Label the Diluent Solution with the Product Name, Batch Number, and Date of Manufacturing.

FILLING RECORD - Liquid, Non Freeze Dried

Product Name _____ **Kit Cat. #** _____
Distributor _____ **Kit Lot #** _____
Theoretical Tube & Vial Yield _____ **Kit Exp. Date** _

SPECIAL INFORMATION _____
_____

IODINE
Batch # _____ **Date Manuf.** _____
Date Received _____ **Time Received** _____

TUBE AND VIAL INFORMATION **Code #** _____ **# Racked** _____
 # Lost _____ **Total # Used** _____

FILLING DATA
Machine(s) Cleaned: **Before Filling - Signed** _____ **Date** _____
After Filling - Signed _____ **Date** _____
Fill Vol. _____ **ml** **Limits ±** _____ **ml** **Filling** _
Batch Vol. ___ **ml** **Leftover** _____ **ml** **Method** _____
 # Tubes or Vials Filled _____ **#Bad Fills** _____ **[ ] Refilled**
[ ] Not Refilled
APU _____ **ml** **TPU ml** _____ **TPR ml** _____

Filling Operators 1) _____ **2)** _____ **3)** _____ **4)** _____
Volumetric Fill Checks: 1) _____ **2)** _____ **3)** _____
4) _____ **5)** _____ **6)** _____ **7)** _____ **8)** _____

Checks done by _____ **Date** _____
CAP AND LABEL INFORMATION

1. Cap Code # _____ **# Used** _____ **# Lost** _
2. Cap Code # _____ **# Used** _____ **# Lost** _
Label Code # _____ **# Used** _____ **# Lost** _

Signed _____ **Date** _____

Checked by _____ **Date** _____
ATTACH SAMPLES OF LABELS

FINISHED PRODUCT RELEASE	Form No.	Rev.	Sheet 1 of 1
Form Approved by:		Date	

ECN notes:

Title: AMYLASE SET

Packaging lot number	Circle one CATALOG Number → AM-389-01 A

The device history documents below were reviewed by → Circle one form number in 2, 5 & 7 below.		MFG ✓	QC ✓
1. Form # 9926	Product flow sheet		
2. Form # 1077 or 1078	Iodine solution		
3. Form # 1082	Substrate solution		
4. Form # 1083	Substrate tube filling sheet		
5. Form # 1084 or 1085	Iodine filling sheet		
6. Form # 1086	Packaging record		
7. Form # QC-PP-07 or QC-PP-01	Finished device specification		

Comments

Sign. MFG Designee No→	APP. Yes or		xxxxxxxxx

Comments

Signature QC Designee No	Approved Yes or	

Production Workmanship and Configuration Sample Tag

PRODUCTION SAMPLE NAME		
INSTRUMENT/PART NUMBER	REV	OPTION CODES
SAMPLE NUMBER		ECN HISTORY ON BACK
NOTES:		

APPROVED FOR USE BY:		Form Number 6-53
PROJECT ENGINEER	Signature Master Sample Only	DATE
LEAD ASSEMBLER	Signature all samples	DATE
LEAD TECHNICIAN	signature all samples	DATE
PRODUCTION MANAGER	signature master sample only	DATE

Back of Sample Control Tag (the above tag)

SAMPLE MODIFICATION HISTORY

Modification Number	ENG (MASTER ONLY)		LEAD ASSEMBLER		LEAD TECHNICIAN	
	SIGNATURE	DATE	SIGNATURE	DATE	SIGNATURE	DATE

SHOP ORDER TRAVELER	S.O.T. NUMBER
	DATE

Form 058-SOT	
Description	Part No.
FROM Department	**TO** Department
Quantity Delivered	Quantity Accepted
Supervisor	Supervisor
Remarks	Lot No. Complete Thru OPN

FOLLOWER TAG		Form 092-FT
Instrument Name		S/N
Line Voltage	Model No.	
Record discrepancies & nature of rework on back		
PROCESS	BY EMPLOYEE	DATE
Assembled		
In-process Check		
Chassis Check		
Test & Calibration		
Burn-in		
Audio Calibration		
Final In-process Inspect.		
Seal Card Cage		
Pre-Cover Inspection		
Final Assembly		
Final Test		
Final Inspection		
Packing/Shiping Inspect.		

9 DOCUMENT AND CHANGE CONTROL

INTRODUCTION

There is no easy way to properly control changes to devices, processes, device master records, etc. Change control is a complex process. Failure to have an adequate change control system can cause equally "complex" results. Inadequate change control exposes a company to product liability actions, results in product recalls, causes internal confusion, and is a serious violation of the Quality System (QS) regulation.

Change control activities and procedures apply to: design; components, including software; labeling and packaging; device manufacturing processes; production equipment; manufacturing materials; and all associated documentation such as quality system procedures, standard operating procedures, quality acceptance procedures and data forms, and product-specific documentation. Change control should also be applied to any production aids such as labeled photographs and models or samples of assemblies and finished devices.

The device master record (DMR) is a compilation of records containing the procedures and specifications for a finished device [820.3(j)]. This record contains the manufacturer’s documentation for the device specifications and all other documentation required to procure components and produce, label, test, package, install, and service a finished device. Manufacturers are to prepare, control changes to, and maintain a device master record using the document controls procedures outlined in 820.30 and 820.40.

CHANGE CONTROL PROCEDURE

Changes to DMR documents shall be reviewed and approved by an individual(s) in the same function or organization that performed the original review and approval unless there is a specific designation that states otherwise. These approved changes shall be communicated to the appropriate personnel in a timely manner. Each manufacturer shall maintain records of changes to documents. Change records shall include:

- a description of the change,
- identification of the affected documents,
- the signature of the approving individual(s),
- the approval date, and
- when the change becomes effective [820.40(b)].

For the medium to large company, a change control procedure is one of a family of standard operating procedures (SOP's) used to produce and control documentation or control activities that result in documentation. The sample engineering change policy/procedure exhibited at the end of this chapter lists a group of six such procedures. However, this chapter concentrates on only one of these -- the change control procedure -- because of the specific requirements for change control in the QS regulation. It is a traditional and current practice for change control procedures to include change control forms. Some manufacturers also use change request forms for suggested changes.

The written change control procedure should describe the company-approved procedures to be followed from the time parts of the device master record are first released for production through examination of a change in relation to other appropriate documents, activities, and implementation. The company procedure should have an appropriate degree of flexibility integrated into it. That is, all changes do not need the same degree of evaluation and approval. Consider manufacturers such as repackers/relabelers that may have to make simple changes such as the size of a container or arrangement of the items in a kit. Also, production runs for some kits may last only a few hours. Obviously, these manufacturers should develop and use a change control procedure that allows rapid changes, approvals, and implementation. The QS regulation is a flexible regulation which allows manufacturers to develop and use procedures that meet their specific needs.

The important point to consider is that all changes are made according to the approved company policy and procedure. A trap that is easy to wander into is the situation where a company, knowingly or unknowingly, allows research and development personnel or other appropriate technical personnel to make changes to a device that is already in production or make changes to an ongoing process without following the approved procedure. Such changes generally do not receive the necessary evaluation and review and, therefore, they may and in many instances have resulted in hazardous or ineffective devices. Making uncontrolled changes is a violation of several sections of the QS regulation, including sections 820.30, 820.40, 820.70, 820.75, and 820.181. Also companies making uncontrolled changes are not operating in a state-of-control. It bears repeating: all changes Should be made according to the approved company policy and procedure.

A change control procedure may be long when a large number of activities are covered. However, a very small manufacturer may have only a few activities. For very small manufacturers, the following are some examples of how to word simple procedures for changing and approving the device master record:

- Draw a line through but do not black out the old information.

- Ink in the new information.

- Date and sign at the change or place a mark at the change which refers the user to the date and signature.

- Ascertain that the modified documents are placed into use and the old documents are removed from production.

- Ascertain that in-process and old finished devices are reprocessed or discarded.

- Record the effective date for these procedures.

The above procedure obviously depends on the devoted attention and knowledge of the person responsible for the change. It is obvious that for a large manufacturer or for complex operations, the person responsible for the change would not or could not “pass the word” to everyone that has a need to know. Hence, the need for written procedures. Small manufacturers, with short communication lines, usually need a less extensive procedure than a large manufacturer; however, the use of a change control form, as described below, by small manufacturers is highly recommended. As the manufacturer grows, all procedures, particularly the change control procedure, should be analyzed and modified to meet current needs. Such a review should be part of the quality system audit.

Change control records for documents should cover:

- identification of the entity being changed,
- a description of the change,
- identification of the affected documents,
- signature of the approving individual(s),
- the approval date, and
- when the change becomes effective.

These elements of a typical change control system are explained below. These controls extend to installation and service when a manufacturer is performing, or contracting these activities.

Identification

The written procedure should cover the identification of the changed device, assembly, component, labeling, packaging, software, process, procedure, manufacturing material and any other related item or document. The change control form should have blanks for recording this data and other data discussed below.

Effective Date

The procedure shall cover the effective date of the change which is usually a completion date, or an action to be performed when a specific event occurs, such as "implement the change when the new mixer is installed, validated, and operational." The blank on the change control form for recording the effective date should not be left empty.

Responsibility

The change control procedure should state which department or designee is responsible for each function to be performed. One of these is the issuance, use, and control of blank and completed change control forms. Another is the extra level of management oversight during the phase-in of a change. (Also see Document Distribution below.)

Revision Level

The way the revision level is to be incremented and which code should be used need to be covered by the change procedure for: components including software, assemblies, and devices; and associated documentation such as labeling, process procedures, and assembly drawings. It is common practice to use numerical revision levels during pilot production and letters during full scale production.

Validation

Each changed device, accessory, labeling, packaging, and process should be thoroughly verified and/or validated by the appropriate department. Then the test results and all information related to the change should be reviewed by the change control board or other designated review group. This procedure is the same as needed for designing and introducing a new product or process into production and is detailed in section 820.30, Design Controls. Changes that only modify documents and do not change any design aspect of a device or process are performed according to 820.40 Document Controls. The change control procedure should state the details of the evaluation and review process or, as appropriate, refer to the company control procedures. The change control procedure should define the responsibilities of the various departments and members of the review board.

Communication

The change procedure should cover the communication of changes to all affected parties such as production, purchasing, contractors, suppliers, etc. As appropriate, activities that apply to internal operations are also applicable to suppliers. Examples are employee training, rework, or disposition of in-process assemblies, use of revised drawings and/or procedures, and disposition of old documents.

Updating Documentation

The change procedure should cover updating of primary and secondary documentation such as instruction manuals. Usually there are no problems with updating or revising primary documentation -- in fact, that is a major reason the given change order is being processed. In contrast, it is rather easy to forget that related secondary documents such as component drawings, instruction manuals or packaging require revision if affected by a given change. The use of a good change control form can alleviate this problem.

Documentation Distribution

Revised documentation should be distributed to persons responsible for the operations affected by the change and old documents removed and filed or discarded, as appropriate. After a document has been approved, these documents shall be available at all locations for which they are designated, used, or otherwise necessary, and all obsolete documents shall be promptly removed from all points of use or otherwise prevented from unintended use. This means current documentation shall be accessible to

company employees [820.40(a)]. Supervisors should be vigilant in overseeing the flow and use of documentation, especially if a change is being phased in, because both the old and revised documentation may exist in a given department during the transition period.

Remedial Actions

Certain changes may affect installation or servicing, or require remedial action in the field or rework of warehouse stock. Changes of this nature should be addressed in the change control procedure. The change control procedure should outline the documentation and activities required for changes involving installation, servicing, or field remedial actions or rework of warehouse stock. (Note that field remedial actions may be classified as recalls depending on the nature of the change. Generally, rework of warehouse stock which is under a manufacturer's control is not classified as a recall.)

Regulatory Submissions

Modifications to devices or manufacturing processes should be made and covered under the quality system change control procedure as described herein. Such changes may also require a premarket notification [807.87(g)] or premarket approval (PMA) supplement (814.20) depending on the classification of the device. The change order or control form is a convenient document for reminding employees that regulatory submissions should be considered when making a change.

Business Factors

In order for the change procedure to be complete, it should also cover other factors such as financial impact, modification of sales literature, update of products in commercial distribution, etc.

QUALITY ASSURANCE REVIEW

Identifying the need for change; making, evaluating, and reviewing the change in the product or process; and revising and distributing the documentation is about half of the change control process--the change also needs to be correctly implemented. Quality assurance and other designated personnel should make certain that the change is fully implemented during routine production, as shown by data and activities that meet GMP requirements for:

- review of production records [820.80(d)(2)];
- acceptance of components, labels, materials, etc. [820.80];
- assuring that quality assurance checks are appropriate and adequate for their purpose and are performed correctly [820.30(d)], [820.181(c)] and [820.80(d)(1)];
- finished device evaluation [820.80(d)];
- collection of device history record data to demonstrate that the device is manufactured in accordance with the updated device master record [820.184]; and
- making certain that only accepted product is distributed, used, or installed [820.80(d) and 820.86].

The change procedure should cover these activities and specify that they are accomplished before the first lot of the changed devices is released for distribution. After the change is implemented, resulting components, in-process items and finished devices should meet the new specifications established in the revised DMR as shown by the data in the Device History Record. This agreement, of course, is assured by the change control procedure as well as the remainder of a manufacturer's quality system.

CHANGES UNDER PREMARKET NOTIFICATION

When making changes to devices and associated manufacturing processes for substantially equivalent devices, manufacturers should consider both Subpart E of Part 807, and Part 820 of Title 21, Code of Federal Regulations, which address Premarket Notification Procedures and Good Manufacturing Practices for Medical Devices, respectively. By considering these simultaneously, labor costs can be reduced and compliance enhanced.

Regulatory Background

Under the Act, the burden is on the manufacturer to determine whether a premarket notification should be submitted for a change or modification in a device. It is not intended that the owner should submit a premarket notification for every change in design, material, chemical composition, energy source, or manufacturing process. Rather it is the manufacturer's responsibility to determine if a proposed change could significantly affect safety or effectiveness. If this change will affect safety or effectiveness, another Premarket Notification submission [510(k)] shall be submitted to FDA. (Please see Premarket Notification 510(k): Regulatory Requirements for Medical Devices, FDA 95-4158 and Deciding When to Submit 510(k) for a Change to an Existing Device.)

Changes in manufacturing processes, labels, packaging, device master record, design, etc., of a device are also subject to GMP requirements in sections 820.30, 820.40, 820..70, 820.75, 820.90, and 820.181. Compliance of manufacturers with these change-control requirements is checked during comprehensive inspections by FDA investigators. Manufacturers may consider their degree of compliance with the QS regulation as one factor, but not the sole factor, when making decisions about premarket notification submissions for modified devices or processes.

Premarket Notification Decisions

Premarket notification submissions are required for changes that could significantly affect safety or effectiveness and for new or modified intended uses. Additional submissions are not required for marketing or convenience changes where safety or effectiveness could not be significantly affected. Management should decide whether or not a change meets the threshold requirements for submitting a new premarket notification. While waiting for an FDA review of the submission, a manufacturer may continue to distribute the unchanged device for its original intended use.

Some manufacturers with highly qualified personnel and substantial experience may feel confident in performing various technical operations and analyzing results to determine that a particular change in a device, component, or manufacturing process will not significantly affect safety or effectiveness of the device. After technical activities are completed and documented, the results should be reviewed by a design-review panel, change control board, or equivalent group. Reviewing changes should include design verification/validation, change control procedures, equipment qualification, equipment calibration, process validation, personnel training, and routine manufacturing procedures. If it is determined that the change(s)

to a previously FDA cleared device could not significantly affect safety or effectiveness of the device, then the intent of the regulation has been addressed and there is no need to submit an additional premarket notification. If this thorough review of proposed changes indicates that a change will significantly affect safety and effectiveness, either positively or negatively then another premarket notification shall be submitted.

Quality System Control Always Required

Section 807.87(g) requires that a premarket notification submission "include appropriate supporting data to show that the manufacturer has considered what consequences and effects the change or modification or new use might have on the safety and effectiveness of the device." Regardless of whether a change is submitted under the 510(k) process, the change should be evaluated under the QS regulation and the associated data filed for an appropriate period of time (820.180) because demonstration of process effectiveness and use of adequate quality assurance acceptance criteria for finished device release are GMP requirements. Change control is also necessary to assure that a modified device or process results in a device that meets company quality claims. Otherwise, the device is adulterated according to Section 501(c) of the FD&C Act.

The above information applies to changes contemplated for devices and associated processes that are subject to premarket notification requirements. If proposed device and process changes are for devices subject to Investigational Device Exemption (IDE) requirements or Premarket Approval (PMA) requirements, then FDA approval should be obtained, in advance, by submitting a supplemental IDE or PMA.

EXHIBITS

An example of a detailed change control procedure and several change control forms are described below and exhibited.

Engineering Change Policy/Procedure

This example of a change control procedure is typical of those used by many manufacturers of electromechanical products. It includes all of the elements described in this chapter and may be used as a guide in developing a change control procedure for medical devices.

Change Control Forms

To aid in the daily use of a change control system, manufacturers often use two forms in conjunction with the change control procedure. Examples of these forms are printed after the sample change control policy/procedures. The first form is called a request for engineering action (REA) or a similar title -- it is a "technical suggestion box." The use of this form encourages all personnel to be involved in product and process improvement, allows management to assign priorities to various tasks, and tends to prevent lack of action. The second form is called an engineering change order (ECO), engineering change notice (ECN), or a similar title. For most manufacturers, the use of ECO paper or computer forms is essential for the implementation and control of all the many elements in a change control system. A log of changes is usually maintained for fast reference to old ECO's and for controlling the issuance of sequential numbers for new ECO's. Also, if used, the completed REA and ECO forms need to be filed as required by the QS regulation in 820.180.

One of the example forms, Engineering Change Package (ECP), is simply an ECO cover sheet for a group of ECO's. An example of a filled-in group change is included. It includes the completed ECP cover sheet and two completed ECO forms. The other three completed ECO forms noted on the example ECP are not reprinted.

The contents of any forms selected for use by a manufacturer and how to use them should be discussed with all affected departments. Manufacturers may use, if appropriate, the example forms as exhibited or modify them to meet their specific needs. In either case, after using an ECO procedure and forms for a few changes to products, processes, and associated documentation, improvements to the form or procedure will become obvious if needed to meet the needs of a specific operation of a company.

COMPANY LOGO

No: _____
Rev: _____
DATE: _____

Sheet 1 of 8

SUBJECT: ENGINEERING CHANGE POLICY/PROCEDURE APPROVED:

_____,
President

1.0 PURPOSE: The intent of this policy is to assure that our products are, and remain, what we intended in our product specifications; are safe, efficacious and reliable; meet the needs of the marketplace; and are cost effective to manufacture and test on a continuing basis.

2.0 SCOPE: This policy establishes the procedures to be followed for engineering changes to devices or manufacturing processes.

3.0 APPLICABILITY: The responsibilities and procedures established by this policy shall apply to all released documents. The policy becomes effective immediately upon approval by the President.

4.0 APPLICABLE DOCUMENTS: The latest revision of the following documents form a part of this policy to the extent specified herein:

No. xxx Document Control Policy/Procedure
No. xxx Document Part Number Policy/Procedure
No. xxx Interchangeability/Compatibility Policy/Procedure
No. xxx Obsolescence Policy/Procedure
No. xxx Change Request Policy/Procedure
No. xxx Design Review Policy/Procedure

(Copies of these procedures and the ECO form discussed below are not included in this Manual. The REA form is reprinted at the end of this procedure.)

5.0 DEFINITIONS

5.1 Engineering Change Board: Each Engineering Change Board Member will represent a major area of activity. The Board will be under the direction of a moderator appointed by the President. The Change Board will meet to review the technical content of all proposed changes to released documentation for accuracy and impact on safety, efficacy, reliability, product cost, parts and finished goods inventory, work-in-process, instruction and service manuals, data sheets, test procedures, product specifications, compatibility with existing products, and other factors listed in _____section of Design Review Procedure No._____.

Sheet 2 of 8

5.2 Change Request: A request for engineering action (REA) may start the change activities. The next stage is the completion of an engineering change request. An engineering change request (ECR) is a completed engineering change order form filled out as described in this policy but unsigned by the Change Board (i.e., is, it is an unsigned ECO form -- there is no ECR form in our company). To merit consideration by the Board, the change request must be complete. Unless the change is so simple that it can be readily understood from the Engineering Change "Request" form, the formmustbe accompanied by a reproducible copy of the last released revision of each sheet of documentation from the device master record that will be affected by the ECR if it is accepted. The reproducible copy must be marked with all proposed changes.

5.3 Engineering Change Order (ECO): An ECO is an ECR (that is, the completed ECO form and associated documents) which has been approved by the Engineering Change Board. An ECOmustpresent a statement of the problem, a solution, updated documentation, an effective date, and a statement that the device and proposed changes meet regulatory requirements.

5.4 Regulatory Compliance: The review by the Change Board includes an analysis of the change with respect to regulatory requirements. For example, the following questions should be answered.

1. Is the change significant enough to require a 510(k) submission?

2. Is there a major change in the intended use? [Requires a 510(k).]

3. Does the change affect our quality system? (A new use such as infusion pumping by an existing precision metering pump means additional GMP requirements may apply.)

4. Do we need to change the labeling in order not to be misbranded?

5.5 Disposition: This action statement defines the updating or disposition of nonconforming materials, components, labeling, software, in-process assemblies, and finished devices at all applicable locations such as suppliers, stockroom, production lines, final test area, finished goods storage, and in field service.

5.6 Effective Date: The effective date will be expressed in terms of shipment date. That is, every change shall be applicable to all units shipped after a specific date. If shipment does not occur by the date specified, an amendment must be issued. The amendment will be presented to the Change Board and upon approval, the ECO cover sheet will be reissued. Quality Assurance has responsibility for verifying that the effective date is met as specified and for maintaining records showing the actual effective date of each change. If a change is not effective by the date specified, Quality Assurance shall be responsible for requesting an amendment to change the effective date.

5.7 Cost: At the Change Board meeting, each department shall be prepared to give the cost impact on its area for implementing each change order. Finance shall assure that all financial implications are considered because the cost analysis must include engineering time, manufacturing time and material, and field service material and labor. The following cost data is to be available at the meeting.

1. Amount of increase or decrease in per unit unburdened material and labor cost. This cost change is not to include extraordinary costs of rework and scrap which are incurred only when the change is first phased in.

2. Total unburdened cost of material to be scrapped in each location indicated on the ECO form.

3. Total unburdened rework cost for all items requiring rework.

4. Total unburdened engineering manpower and material required to design, test and document the change.

5. Where rework or replacement of units in the field is involved, Field Service must indicate the proportion of costs to be charged to warranty expense.

5.8 Amendment: An amendment may be issued only to change the effective date or correct drafting errors in implementing the change order. Any Board Member may request that an amendment be issued.

5.9 Board Member: An Engineering Change Board Member shall be a person appointed by the area manager to represent a particular functional area. A Board Member may represent more than one functional area. For changes to a process, or design of a device, labeling, or packaging, board members must at least include a design review to meet the following GMP requirements:

- Each manufacturer shall establish and maintain procedures to ensure that formal documented reviews of the design results are planned and conducted at appropriate stages of the device's design development.

- The procedures shall ensure that participants at each design review include representatives of all functions concerned with the design stage being reviewed, as well as any specialists needed.

- The results of a design review, including identification of the design, the date, and the individual(s) performing the review, shall be documented in the design history file [820.30(e)].

5.10 Alternate: Each functional area shall also designate an Alternate who shall be available to attend Change Board meetings in the event that the Board Member is not available. Each functional area is to notify the Change Board Moderator of the names of its Board Member and Alternate.

6.0 RESPONSIBILITIES

6.1 Engineering Change Board Moderator: The Engineering Change Board will meet at the discretion of the Moderator. The Engineering Change Board Moderator is responsible for the conduct of the Change Board meetings. This person is appointed by the President for an indefinite term. At least one full working day before each meeting of the Change Board, the Board Moderator shall distribute to all Board Members a copy of all ECR's to be discussed at the next meeting of the Board.

6.2 Engineering Change Board Members: Engineering Change Board Members shall be responsible

for the functional areas they represent in all matters relating to engineering changes and shall be empowered to act on behalf of their areas in Board actions. The Board Members or Alternates shall come to each
meeting thoroughly prepared to discuss each Engineering Change Request (ECR) to be discussed. Specific Board Member responsibilities are listed below.

Product Management - Product Management shall determine the effect of changes on marketability, field information, catalogs, price lists, data sheets, and gross profit margin. Product Management must verify the suitability of each design (not documentation only) change in the international as well as the domestic marketplace.

Field Service - Field Service has responsibility for determining the: time required to implement the change in the field; availability of components and assemblies for retrofit; impact of the change on service manuals; and adjustments to service stock. Field Service will make the changes in the areas under their jurisdiction and pass other defined tasks to appropriate departments.

Quality Assurance - Based on verification data, analysis and design reviews, Quality Assurance and manufacturing engineering shall be aware of the effect of all changes on test requirements and on overall quality of our products and assure that product specifications are met. Quality Assurance shall assure that there is compliance with customer, corporate and regulatory agency requirements.

Manufacturing - Manufacturing shall determine component and raw material availability, break-in point, effect on material-on-order, material-in-process and material-in-stock. Manufacturing engineering shall assure that manufacturing and test procedures are adequate. Manufacturing shall determine total cost to the Manufacturing Department of implementing each change.

Engineering - Engineering is responsible for making certain that the change is technically feasible and complies with appropriate company and customer specifications and with accepted standards. Every major change must be fully analyzed and tested (verified) and the results documented by Engineering before it becomes a change order. Any Change Board Member may request that Engineering furnish evidence of technical viability of a change. If the Board so decides, a change may be tried in Manufacturing on a limited pilot production basis before final approval and implementation in full-scale production. None of the trial units may be shipped until the change has been verified; validated, if appropriate; subject to design review; and received final approval. If, as the result of such trial production, the change is altered or modified before final approval, all of the trial units must be changed to the final form before shipment.

Engineering shall supply QA and Manufacturing Engineering with copies of verification protocols, if any, to be used to update production test methods. The updated production documents are part of the change.

Finance - Finance shall make certain that all financial aspects have been considered.

6.3 Engineering Documentation Section (Engineering Services): Engineering Documentation Section shall have overall responsibility for coordinating, scheduling, and executing documentation changes.

7.0 PROCEDURE: The procedure followed for a given change depends upon whether the change is only to documentation or is a change that affects design, the manufacturing processes or just

documentation.

7.1 Procedure for Design and Process Changes

1. A request for engineering action (REA) is completed and forwarded to the Manager of Engineering Services. (The REA form is reprinted at the end of this procedure.)

2. A number is assigned and appropriate audit controls are established. Engineering Services then sends a copy of the REA to the cognizant device or process design section for recommended solutions, evaluation of impact on specifications, and a recommended effective date. As appropriate, the changes must be supported by device verification data and/or process evaluation data or validation data. The REA is then forwarded to the Engineering Documentation Section.

3. Upon evaluation for adequacy of data, where-used considerations for the items being changed are made. Engineering Services makes certain that the latest revision of all affected documentation is included. If not already done, an "ECR" (unsigned ECO) form is completed at this stage.

4. Sepias (or separate computer versions in a computerized system) are made of all affected documents. The ECR number and proposed changes are marked on the sepias. These sepias are included as part of the ECR. The only exception from this procedure is where the change is basically self-explanatory, i.e., where all necessary information can be discerned from the section on the ECR form indicating "change from" and "change to."

5. The Engineering Documentation Section will then duplicate and distribute copies of the ECR to each Change Board Member. Upon receipt of the ECR, each Member shall review the proposed change and determine the impact on their area.

6. The Change Board Moderator then calls a Change Board Meeting.

7. All aspects of the change request are reviewed at the meeting including the following: Is the ECR presented so that anyone may understand the problem and the solution? Does the verification data show that the device meets the device product specification? Does the device continue to meet the intended use and the needs of the user/patient? Has all documentation including manuals and data sheets been updated?

The Board will then establish a reasonable effective date. Finance will make certain that all costs of this change have been considered. After agreeing upon an effective date, each Board Member signs the change request. Each signature implies concurrence with the method of solution, effective date, and costs. If the Board Members are unable to reach a unanimous decision, the issue is submitted to the President for resolution.

After all Board Members in attendance have signed, the ECR becomes an engineering change order (ECO). Copies of the cover sheet may be issued by Technical Services upon request of the Board Members if the effective date is very near and the Change Board has not modified the ECR before approval. This action permits Manufacturing to use the previously distributed marked-up sepias or "from-to" information on the ECR as operating documentation until copies of the updated original documents are available for distribution.

It is the responsibility of Manufacturing to indicate the earliest permissible effective date in all areas, i.e., supplier, stockroom, raw material, and work-in-process. It is the responsibility of Field Service to indicate an effective date for any field activities.

8. The change order is then sent back to Technical Services where copies are made for the Board Members, who requested them. Upon completion of this task, the master documentation is withdrawn from the print file, updated to the new revision, and copies are distributed and obsolete documents are collected. During the updating process, a copy of the marked-up sepia (if any) replaces the master in the print file.

9. After all documents are updated, the change order is filed permanently in the design history file for the device. The verification protocol and data and design review documents and minutes are also placed in the design history file.

7.2 Procedure for Minor Changes and Changes in Documentation Only.

This procedure is the same as that for design changes except that the second and third steps read as follows:

2. A number is assigned and appropriate audit controls are established. Upon evaluation for adequacy of data, where-used considerations are made. Technical Services assures that all affected documentation is included and that it is the latest revision.

3. Technical Services then sends a copy of the ECR to the Design Section for evaluation of the effect of the changes on the device and for recommendations on the effective date to be suggested to the Change Board. The ECR is then returned to Technical Services.

8.0 ENGINEERING CHANGE ORDER FORM (ECO): A definition of the various items on the form and instructions on completing each item follows.

1. **Status:** At the top of the form are the words "Engineering Change" followed by two words, REQUEST and ORDER. When the mark appears in the request area or the form is not signed by the Board Moderator, it shall be considered a request or preliminary copy -- not an action copy. The change order is an action copy which must bear the signature of all Board Members or their Alternates. (The Moderator is empowered to sign for any function not represented at a meeting.)

2. **Amendments:** Amendments shall be designated by an alpha suffix, e.g., A, B, C, etc.

3. **Originator:** The individual who initiated the REA that resulted in the ECR or ECO.

4. **Interchangeability/Compatibility:** This area is made up of two blocks. First block is "Yes", second block is "No". Interchangeability/Compatibility is expected to be checked off as "Yes" when it affects form, fit, or function of any numbered part. (The design, design verification and design review must always consider interchangeability and compatibility.)

5. **Change Complete Block:** The drafting supervisor shall sign this block when the documentation is updated.

6. **Prerequisite:** Is there another ECO or new Product Release Notice which must be effective before this change can be implemented? If so, what are the numbers?

7. **Reference:** In this block will be listed any references such as REA's, etc.

8. **Device Affected:** This block is used to indicate which device(s) or device line is affected by this particular change notice.

9. **Description of the Problem:** The description must be presented so it can be fully understood by the technical personnel involved.

10. **Solution:** The solution is what has to be done to correct the problem. It must be explained in terms that can be fully understood by our technical staff

11. **Item Number:** A sequential number beginning with 1.

12. **Size:** The size of the sheets of the drawing or procedure.

13. **Revision:** From what revision level the document is leaving and to what revision level it will go.

14. **Description:** This section must contain a general description of the drawing, not necessarily its title.

15. **Where Used:** To which device(s) or processes do the changes apply? This information is especially important if a component is used on several devices.

16. **Disposition:**

    1. Engineering Cost: List engineering cost of design and documentation change.

    2. Supplier: What needs to be done to update in-process assemblies at a supplier, i.e., rework, use as is, or scrap?

3. Stock Room: What should be done with non-conforming purchased components in our stock room? By what date should the above action be complete?

4. Work-in-Process: What do we wish to do with the material on the floor?

5. Finished Goods: What do we do with the material in finished goods?

6. Field Service: What should be done to devices in the field?

7. Cost: Each department is responsible for reporting the cost of the change with respect to its area.

17. Effective Date: Each change shall be applicable to all units shipped after a particular date where the date is relatively unimportant because the change is a minor documentation change. In all other changes, an effective date must be assigned by the Board. If it is important to a particular functional area that a change be implemented by a date or not sooner than a date, it is the responsibility of the appropriate Board Member to assure that an acceptable effective date is designated.

The change notice is broken into Parts 1 and 2. Part 1 shows how to update the documentation. Part 2 is the special rework instructions required by Manufacturing or Field Service Operations on how to update a component or assembly that does not conform to the new revision.

(Note: The specific ECO form for this procedure is not included in this manual. However, several ECO forms follow. One of the example forms, Engineering Change Package (ECP), is simply an ECO cover sheet for a group of ECO's. An example of a filled-in group change is included. It includes the completed ECP cover sheet and two completed ECO forms. The other three completed ECO forms noted on the example ECP are not reprinted.)

REQUEST FOR ENGINEERING ACTION		REA No.
Originator	**Dept**	**Date**
Component, subassembly, or device:		
Drawing(s)		
Problem (in detail)		
Solution recommended, if known	**Date action required by**	
Comments		
Dept Manager approval		**Date**
Assigned to	**Date forwarded for solution**	
SOLUTION	**Charge No.**	**Priority**
App. By	**ECO Number**	**Date**

Not es on back? YES __ Sheets attached? YES

PROCEDURE

1. **Originator: Complete top of this form except for REA number.**
2. **Obtain your Department Manager's approval.**
3. **Forward original to Technical Services Manager who will assign the REA number.**
   Note: One copy will be returned to originator with REA number assigned.
   If problem involves safety, effectiveness, or reliability, Technical Services will forward to the QA Manager a copy with the REA number assigned.
4. **Technical Services takes appropriate action and also executes an ECO.**
5. **Technical Services returns a copy to Originator after resolution of problem.**

Form No. _____ Rev. _ App. By _____ Date

COMPANY LOGO	Engineering Change Order (ECO)	ECO #

Signatures	Date	Approvals	Date	Reason for Change
Originator		Type A		[ ] Improve process [ ] Biocompatibility [ ] Design improvement
Project Engr.		Type B		[ ] Correct error [ ] Cost reduction [ ] Customer request
TYPE A[ ] B[ ] C[ ]		Type C		[ ] Labeling or packaging [ ] Regulatory

DESCRIPTION OF CHANGE	Action Code	Drawings Affected	REVISED From	To

Change action required		codes	Change action required		codes
Purchasing and Production	Rework components in stock	1	Service and Repair	For reference only	8
	Rework part in-process	2			9
	Scrap in-process items	3			10
	Make new	4	Other	Labeling Change Parts in Field	11

	parts		Action		
	Rework finished goods	5		Packaging Notify User of Part	12
	Notify supplier	6		Employee training	13
	See old parts for spares	7		510(k) required for Change	14

10 PURCHASING AND ACCEPTANCE ACTIVITIES

INTRODUCTION

This chapter covers component specifications, supplier assessment, receiving components and the services rendered in manufacturing medical devices. Manufacturers of medical devices should maintain a consistent, systematic quality system which, along with other quality assurance activities, should assure that all components, materials, and services involved with the manufacture of medical devices are acceptable for their intended use. This control is a combination of: component and supplier selection and verification; data collection, analysis and corrective action; supplier, contractor, and consultant assessment; identification and status of product including labeling and/or quarantine; and operational procedures.

The establishment and maintenance of requirements, including quality requirements, is essential for the manufacturer when dealing with component suppliers, consultants, and contractors [820.50(a)]. The ability to meet specified requirements is important when evaluating the suppliers and service providers. Assessments of these providers shall be maintained and documented. Possible appropriate methods of accomplishing these goals include audits, checking with other clients, and previous performance data. If prior assessment is not possible, then the manufacturer should assess the service as it is being performed. Assessment shall be documented. Procedures for accepting incoming product shall also be established and maintained. Various acceptance activities may include inspections, tests, and other forms of verification. Acceptance or rejection of components and services shall be documented (820.80).

Components

"Component" is defined in 820.3(c) of the Quality System (QS) regulation as any material, substance, piece, part, software, firmware, labeling, or assembly, which is intended to be included in the finished, packaged, and labeled device. For example, fasteners, blood tubing assemblies and labels are components. This definition excludes "manufacturing materials," which by definition, are not intended to be included as part of the finished, packaged, and labeled device.

According to 820.3(p), "manufacturing material" is any material or substance used in or used to facilitate the manufacturing process, a concomitant constituent, or a byproduct constituent produced during the manufacturing process, which is present in or on the finished device as a residue or impurity not by design or intent of the manufacturer. Examples of manufacturing materials include: cleaning agents, mold-release agents, lubricating oil, or other substance used to facilitate a manufacturing process which is not intended by the manufacturer to be included in the finished device.

Manufacturers of components sold only for further manufacturing of a medical device are not required to comply with the GMP requirements for finished devices. Many components of devices, such as transistors, containers, hardware, etc., are readily available in the marketplace and are not

manufactured exclusively for use in devices. Many of these manufacturers supply only a small fraction of their production to finished device manufacturers. However, section 820.1 of the Quality System regulation encourages component manufacturers to use applicable GMP elements as guidance.

If a component is manufactured in the same or proximal facility, and produced for use in finished medical devices, then the component is considered part of the production of the finished devices and is subject to the applicable requirements of the GMP requirements. If the component is manufactured in a separate plant owned by the finished device manufacturer, then the manufacturer has flexibility in handling the quality assurance activities related to the control of components. One satisfactory approach is to have the plant that builds the components operate in full GMP compliance. Under this arrangement, the plant which does the final device assembly would still be responsible for ascertaining that the quality and integrity of incoming components have not been damaged during shipment. Alternately, the component manufacturing plant may not fully comply with Quality System regulation. Then the plant that does final assembly should handle the acceptance of these components with the same degree of control as if the components were purchased from an outside supplier.

For components such as labels, package inserts, packaging, etc., there is additional information in chapter 11, Labeling; and chapter 13, Packaging.

Accessory Devices

The Quality System regulation applies to manufacturers who produce finished accessories to devices intended to be used for health-related purposes. An accessory is any finished unit distributed separately but intended to be attached to or used in conjunction with another finished device. Therefore, any manufacturer of accessory devices should meet all FDA regulations for a finished device. These regulations include 21 CFR Part 807 Subpart E, Premarket Notification; 21 CFR Part 807 Subparts B, C., and D, Registration and Listing; 21 CFR Part 820, Good Manufacturing Practices (GMP); 21 CFR Part 801, General Device Labeling; 21 CFR Part 809, In Vitro Diagnostic Labeling (if applicable); etc.

Contractors and Consultants

Contractors and consultants generally provide a service rather than a physical component. This service should be treated in basically the same manner as physical components because these services affect the quality of the finished device. The combination of both services and physical components determines the quality of the finished device. Services should be obtained per 820.50, Purchasing Controls, and be controlled upon receipt using the applicable requirements in 820.30, Design Controls, 820.70, Production and Process Controls; 820.80, Receiving, In-Process, and Finished Device Acceptance, etc., depending on the nature of the service.

COMPONENT SELECTION AND VERIFICATION

Verification of physical components is a very important step toward producing a high quality product. Verification of components consists of determining through documented testing that a component will perform its function reliably in the intended application and under the most adverse environmental conditions in which the device is expected to be used. These conditions shall consider

the needs of the user and patient [820.30(c)] and shall encompass the manufacturer's labeling claims for the device.

Components have to be carefully selected, using the requirements of the device as a guide. Components should be chosen so that they will not be over-stressed and will be compatible with the internal device environment, as well as the external environment that the device is expected to encounter during manufacture, distribution, and use. The components should then be appropriately tested, alone, and as part of the device, utilizing the specifications established for the component and the device. New components or components used in an unusual application will usually need extensive evaluation. This evaluation should include parameter and life testing as well as compatibility testing for both the internal and external environment. Well known industry standard components that are used in their normal application and that are not over-stressed will need only minor testing, which is usually an integral part of the verification of the device design. A record of any component verification testing should be maintained. This record should include the component identity and the testing methods that were used, as well as the actual test data and results.

PURCHASING AND RECEIVING OF PRODUCT

Component quality is maintained through correct specifications, procurement, incoming acceptance, storage, handling, installation, and change control. To monitor the adequacy of these activities and procedures, feedback from the quality system is needed. Corrections are made if necessary. In addition to maintaining quality, the manufacturer shall also establish and maintain procedures for identifying product during all manufacturing stages from receipt through installation (820.60 and 820.86). Product includes components, manufacturing materials, in-process devices, finished devices, and returned devices.

Specifications

Component specifications are required as part of the device master record. Components are selected and their specifications are documented during the design of the device. The specifications should be well designed, achievable, and acceptable to suppliers. They should adequately describe the quality characteristics, dimensions, design, materials, performance, and any other features necessary to assure receipt of the item desired. For unusual, vital, new or key components the specification data is derived primarily from the verification data with minor details from the catalog data. For routine components, such as those that have been used for a long time or have a known performance history, a catalog designation may be adequate to describe a component and assure its purchase. For some components such as transistors, the catalog number also may be used to obtain complete specifications from a reference manual. Specifications should reflect both design requirements and quality/reliability needs. The quality level for each component should be specified. Components usually are available in several quality levels such as reagent grade, commercial grade, military grade, etc. In some cases, a significant increase in component quality can be obtained for a modest increase in cost by specifying a higher grade, thus reducing the probability of future quality problems and the possibility of significant associated costs.

Supplier Qualifications

A major factor in obtaining high quality components is the selection of suppliers. Although a manufacturer's knowledge of supplier operations may be limited and information about the operations difficult to obtain, the GMP requirement that a manufacturer is responsible for quality remains undiminished. To the maximum extent feasible, selection and qualification of suppliers by audits, performance analysis, etc., should be part of a quality system. If the manufacturer does not have the capability to test components for conformance to specifications, then supplier test data or outside lab results are acceptable provided that components are tested and inspected in a statistically valid manner to show their acceptability for use in the finished device. Any outside test results should be accompanied by relevant raw data used for the test so that judgments of authenticity may be made by the finished device manufacturer. Excluding a supplier whose components are unreliable from supplying components may help prevent problems with the final device and is certainly worthwhile as a cost reduction effort.

It is important to remember that raw components acquire cumulative value as they are processed through receiving, assembly, test, inspection, and as they ultimately become part of the finished device. If a component fails during assembly, or as part of the device, additional costs will be incurred for fault isolation, removal, replacement, inspection, testing, etc. When field failures occur, the ultimate cost of the component becomes even higher because its replacement requires travel, trouble-shooting, and retrofit. In addition, customer dissatisfaction, user injury, product liability action, medical device reporting, or regulatory action may result. Usually, the initial cost of a component is relatively insignificant compared to the later cost should the component prove to be defective or improper for the selected use. Many recalls occur because manufacturers fail to qualify components properly or to assure that a supplier's manufacturing methods and quality system are adequate.

Acceptance Procedures

Written instructions are necessary to assure that components, manufacturing materials, etc. are properly identified, processed, and stored when received. Written inspection and test procedures are necessary to prescribe the:

- **acceptance activities performed;**
- **dates acceptance activities are performed;**
- **the results;**
- **signature of the individual(s) conducting acceptance activities; and**
- **where appropriate, the equipment used.**

Before acceptance, all components should be either physically separated (quarantined) or clearly identified as not yet accepted. The decision to separate or tag not-yet-accepted product should be made based on the characteristics of the device, the potential for mixups, plant conditions, and manufacturing practices.

Although 820.80 requires a written procedure for accepting components, the Quality System regulation in 820.5 allows discretion in the quality system. Thus a very small manufacturer, usually 10 or fewer employees, may only need very brief written acceptance procedures referencing the purchase orders and receiving tickets. As the size of the operation, the numbers of activities, and number of people involved increase, the need for comprehensive written instructions generally increases.

Acceptance Criteria

Manufacturers should have specific acceptance criteria for components. Acceptance criteria are the attributes of a component that determine its acceptability, such as appearance, dimension, purity, performance characteristics, etc. Typically, acceptance criteria are made a part of the inspection/test procedure. For example, if component specifications or a drawing adequately describe the attributes needed in order for the component to perform in its intended manner, these may be used as the acceptance criteria. If components or the suppliers of the components have a history of good performance, the components may be accepted for use after a visual check to assure they are the items intended and that they are not damaged or contaminated. Components, which need only a visual inspection, may be accepted using the purchase order data as acceptance criteria. The purchase order and/or receiving ticket should at a minimum contain the following information:

- **name of supplier;**
- **description of the component or other product; and**
- **quantity shipped.**

For a standard component, the catalog number may be used as a description. QA personnel should determine whether the use of any "abbreviated" criteria are adequate during their audit of production rework, history records, complaint files, and service records.

Testing and Inspection of Product

The minimum acceptance activity per current practice requires that all incoming components and other product receive at least a visual inspection for contamination and/or damage and be identified as the component specified on the purchase order. A manufacturer accepting the product has the discretion to determine when and where product should be inspected, sampled, and tested for conformance to specifications depending upon the risk that failure of that component may pose. As appropriate, product may be tested and/or inspected by:

- **the supplier;**
- **when received;**
- **during manufacture of the device; or**
- **as part of the finished device.**

If components are tested as part of the finished device, the testing should be able to reveal failed and "out-of-spec" components and not just that the finished device does not meet specifications. This determination, of course, may be performed after removing the component from the device. The rejection shall be documented [820.80(b)].

Manufacturers who decide not to sample or test specific components should be able to justify that decision based on such factors as knowledge of the supplier's previous performance in providing high quality components, the component performance history, and application of the components in the device. Manufacturers may rely on component suppliers to conduct testing if the manufacturer specifies or is knowledgeable about the supplier's quality system, particularly the inspection and test programs and the supplier has specifications that properly define the manufacturer's acceptable limits for the component or material parameters. These specifications may be used to meet the

device master record requirements for component specifications, if these accurately reflect the parameters, composition, and configuration required for the component to perform the function for which it was selected. Supplier specifications are usually adequate for standard components. However, a manufacturer who relies on supplier specifications usually has no control over changes in these and, therefore, should assure at an appropriate point in the manufacturing process that the components received meet the desired specifications.

If components are tested by the supplier, acceptance of components can be based on certification and review of test data submitted by the supplier for the specific components provided. Certification should accompany each lot of components. When certification is used, the manufacturer should periodically verify the validity of the certification through an assessment of the supplier.

Where historical data shows that certain components or other product have been substandard and resulted in a device failing to meet specifications, or where performance history has not been established, specific steps should be taken to assure components meet specifications. Typically, this task is accomplished by sampling and testing each lot of components to assure that the components meet specifications. Where appropriate, all significant or high risk components should be sampled and tested.

Manufacturers may test entire assemblies of components rather than individual components. If, however, testing an assembly cannot assure fitness-for-use of the components, then components should be tested on an individual or lot basis, whichever is appropriate. For example, assemblies with an internal feedback circuit could have a very marginal component. Because of the circuit design, the condition of the marginal component might not be detected by testing the entire assembly. Therefore, the feedback loop in the assembly should be opened during one of the tests, or the individual components should be tested.

When using a contract laboratory to test production components, the laboratory becomes an extension of the device manufacturer's quality system. The device manufacturer is responsible for assuring that the contractor's test and inspection procedures are acceptable. This assurance maybe obtained by audits of the laboratory, by the lab staff, and by the finished device manufacturer.

Inspection and testing will not improve the quality of components or other product; however, if the inspection and testing is appropriate and performed adequately, these activities can be used to prevent or significantly reduce the use of low-quality or defective product. Through feedback into the overall quality system, data on products will help identify basic causes of problems and lead to solutions (820.100). If problems are found, actions such as design changes, tighter acceptance criteria, supplier assessments, or change of suppliers may be appropriate.

Acceptance and Rejection Records

Adequate records shall be maintained to provide objective evidence that components were inspected and accepted, or rejected. These records are a part of the device history record and should be maintained in a format that facilitates review. The records, however, are not required to be maintained in a single file with other production history records, and are typically filed in the receiving or quality control area according to part number or component nomenclature. Small manufacturers may use purchase orders or packing slips to record acceptance and rejection if they contain adequate information.

The Quality System regulation specifies in 820.80(b) that a record of component acceptance and rejection be maintained. Typically, acceptance/rejection records should contain:

- **acceptance or rejection documentation;**
- **number and type of deficiencies;**
- **quantity approved;**
- **quantity rejected; and**
- **nature of corrective action taken.**

Obsolete, Deteriorated, and Rejected Components

Obsolete, deteriorated and rejected components shall be identified (820.60, 820.86, and 820.150) as such and be placed in a separate quarantine area or specially identified area to prevent mixups. If practical, components should be individually identified as rejects. Where it is not feasible to tag each rejected component, as in the case of transistors, bolts, bottles, etc., containers or packages of rejected lots should be clearly marked and otherwise appropriately segregated from accepted components. See 820.86 for clarification. Manufacturers should determine the need for a separate written procedure for handling these components based on the size of the manufacturer and complexity of their devices and operations. Disposition of nonconforming product shall be documented [820.90(b)].

Records for rejected components should state whether the components were returned, scraped, reworked, etc. In very small manufacturers, disposition can be recorded directly onto the purchase order, receiving ticket, or other associated document. Small-to-medium sized manufacturers generally record disposition on the form used to receive components. Most large manufacturers record disposition of rejected components on standard forms such as a Nonconforming Material Report (NMR).

When components, materials, etc., become obsolete, many manufacturers assign new identification numbers to the new version of these components etc. The obsolete items are retained for other uses, such as repair parts, engineering projects, etc. In these cases, the old and new items should be adequately segregated and/or identified to prevent inadvertent use of obsolete components in production.

Component Storage

Each manufacturer shall establish and maintain procedures for control of storage areas and stock rooms for product to prevent mixups, damage, deterioration, contamination, or other adverse effects pending use or distribution and to ensure that no obsolete, rejected, or deteriorated product is used or distributed. When the quality of product deteriorates over time, it shall be stored in a manner to facilitate proper stock rotation, its condition shall be assessed as appropriate. 820.150 procedures shall be established and maintained that describe methods for authorizing receipt from, and dispatch to, storage areas and stock rooms.

Although not a direct requirement, all raw materials and components used in the finished device should be received through a central control point. Centralized receiving leads to orderly storage, limits access to stored material, and aids a manufacturer in meeting other GMP requirements.

Components and other product should be identified or stored so that it is obvious at all times that product has been accepted, rejected, or is awaiting a disposition decision. A quarantine area can be either a physically secure area or simply limited access area identified as a quarantine area. If special environmental storage conditions are required such as for many biologically derived components, these conditions should be controlled and monitored and the associated specifications included in the device master record.

When the device is to be sterilized, storage conditions should be selected, as appropriate, to prevent contamination of components and packaging by bacteria or filth. Also, temperatures should be controlled as necessary to prevent or reduce the growth of bacteria. The higher bioburden (bacteria, etc.) levels may challenge the sterilization cycle to an extent greater than the capability established during process validation and, thereby, result in a sterility assurance level that may not meet the finished device specification. Some components, particularly those used in the manufacture of in vitro diagnostic devices, if not stored properly, may support growth of bacteria.

Component Traceability

The criteria as stated in 820.65 for determining the need to have traceability via a unit, lot, or batch control number of a device specifies devices intended for surgical implant into the body or those that support or sustain life and whose failure to perform, when properly used in accordance with instructions for use provided in the labeling, can be reasonably expected to result in a significant injury to the user. Identification of traceable devices should be based on the health hazard presented if a device fails to meet its performance specifications when operated as intended. Because of the design control requirements (820.30), user error and the environment are not considered by FDA as a means for excusing the lack of device performance. User error is not a performance failure, although it could be considered a result of inadequate directions for use, other inadequate labeling, or poor human factors design. The environment could result in failure of a device but it should not effect the result of the device failure.

FDA is concerned about the failure of components that would result in sudden or catastrophic device failure, which can reasonably be expected to result in significant injury to the user, such as:

- **no output from an implantable cardiac pacemaker;**
- **fracture of an implanted orthopedic implant;**
- **runaway in an implanted cardiac pacemaker;**
- **misfiring of a synchronized defibrillator; etc.**

A manufacturer should know in detail how the device functions and the purpose of each component in the finished device. If as a result of a failure, the performance, lack of performance, or effect on safety or effectiveness of the finished device could result in significant injury to the user when the device is properly used in accordance with instructions in the labeling, the component under consideration may require increased control and traceability. The effect that each component will have on finished device performance, should the component fail to perform as intended, should be determined. Thus, manufacturers should carefully study the possible failure modes of their devices and decide which components are truly critical under the various modes. This determination may be time-consuming with respect to some devices, but it is necessary. It will, in the long run, save manufacturers liability, repair, and replacement costs. To make such a determination,

manufacturers should conduct reliability tests and failure effects analyses during the design phase in order to accurately identify critical components.

The number of components that need to be considered as potentially needing to be handled as traceable components can be reduced by considering the reliability of components and whether they "reasonably" can be expected to fail. For example, power cords, clamps, plugs, etc. seldom fail. Therefore, manufacturers may not need to consider extensive tracing requirement of these components. Also, manufacturers can consider a subassembly as a component and, thereby, reduce the number of identification and record keeping activities, but all rationale and justification should be documented.

Written Test Procedures

A device manufacturer shall establish and maintain procedures to ensure that all purchased and otherwise received product conforms to specified requirements (820.50) and establish and maintain procedures for acceptance activities [820.80(a)]. The manufacturer shall assure that all lots of components or other products are accepted, sampled, tested and/or inspected using written procedures. The inspection/test procedure for each component shall be correct [820.30(d), Design Output and 820.30(h) Design Transfer], dated, and approved. The design verification procedures usually may be used to develop production test procedures. The procedure should specify, as appropriate,:

- **items to which it applies,**
- **product characteristics to be inspected/tested,**
- **acceptance/rejection criteria,**
- **test method(s),**
- **data forms,**
- **sampling plans, and**
- **necessary test inspection equipment and tools.**

Sampling Plans

When assuring that components and other products meet acceptance criteria, manufacturers may test either all components or may test a portion of the components using a sampling plan based upon an acceptable statistical rationale (820.250). A manufacturer shall be prepared to demonstrate the statistical rationale for any sampling plan used. Plans should be developed by qualified mathematicians or statisticians, or be taken from established standards such as ANSI Z1.4. It should be recognized that all sampling plans have a built-in risk of accepting a bad lot.

This sampling risk is typically determined in quantitative terms by deriving the "operating characteristic curve" for the selected plan. Each sampling plan has a characteristic curve. ANSI Z1.4 contains operating characteristic curves for sampling plans presented in the standards, and it can be used to determine the risk a sampling plan presents. A manufacturer should be aware of the risks the chosen plan presents. Operating characteristic curves are a means of graphically showing the relationship between the:

- **quality of lots submitted for sampling inspection, usually expressed in percent defective, but may be expressed in defect per hundred units; and**

- **the probability that the sampling plan will yield a decision to accept the lot, described as the "probability of acceptance."**

Control Numbers

Manufacturers of surgically implantable or life sustaining devices whose failure to perform when properly used can be reasonable expected to result in a significant injury shall establish and maintain procedures for identifying with a control number each unit, lot, or batch of finished devices and when appropriate components. Control numbers should be assigned to each unit, lot or batch of components that were manufactured under similar conditions over the same time period so that defects can be traced to the component manufacturer and the cause of the defects determined and corrected. If a subassembly is regarded as a traceable component by the manufacturer, a control number for that traceable subassembly shall be recorded in the device history record.

CONTRACTOR AND CONSULTANT ASSESSMENTS

Manufacturers shall establish and maintain the requirements, including quality requirements, that will be met by contractors/consultants that perform a service for them. To aid in accomplishing this task each manufacturer shall:

- **evaluate and select contractors/consultants based on their ability to meet specified requirements, including quality requirements. This evaluation shall be documented.**

- **define the type and extent of control to be exercised over the contractors/consultants based on the evaluation results.**

- **establish and maintain records of acceptable contractors/consultants.**

Contractors and consultants often provide information or a service rather than a physical component. However, the thought and control processes are similar whether one is working with services or with physical product. The input from contractors and consultants have a definite impact on the finished device. Services may include: design activities, various product verification/validation activities, sterilization, routine maintenance, and calibration of equipment.

Each manufacturer shall provide adequate resources and trained personnel to properly assess the activities of their contractors and make adjustments as necessary. Contractors and consultants maybe assessed based on their applicable education, experience, ability, resources such as facilities and equipment, list of clients, patents, technical reports, etc. Assessment may include conducting internal quality audits [820.20(b)(2)]. Therefore, each manufacturer that is having important work done by a contractor should inform the contractor that their quality system and activities may be audited. These services may include janitorial, consultants, design work, calibration, sterilization, laboratory, and maintenance.

Interface Requirements

At various stages of product development the manufacturer may need to interface with different

groups. If a need for this interface relationship arises during the design phase, a plan shall be developed describing the interface with different groups or activities during the design process [820.30(b)]. By planning for outside services, and including these providers in selected design review meetings, a manufacturer increases the probability of receiving a service that meets requirements. Also the manufacturer is held responsible for work done by outside contractors or consultants. Thus, it is in the manufacturer's best interest to keep providers adequately informed and to monitor contractors to ensure that the correct design, production, or process controls are applied to contractor services to ensure the service or finished product conforms to its specifications (820.30, 820.50, 820.70, and 820.80).

Process Validation Requirements

Regardless of whether a manufacturer or a contractor performs the actual work, the manufacturer is responsible for establishing and maintaining control of the process parameters for the validated process (820.75). Established procedures for validation and the validation results should offer a high degree of assurance that the process consistently produces an output that meets pre-established specifications. Validated processes shall be performed by a qualified person(s) and be documented regardless of whether the manufacturer or an outside contractor performs the validation activities. For more information see Process Validation, chapter 4.

Device Servicing Requirements

If a manufacturer contracts for device service with another party, the assessment and selection of such contractors shall be done according to 820.50 Purchasing Controls. Such service activities and reports should be periodically reviewed to assure that the service activities meet GMP servicing requirements as briefly described below.

Device servicing performed by contractors and/or consultants shall be conducted using established procedures for performing and verifying that the service meets specified requirements (820.50 and 820.200). A written report on the servicing shall include:

1. **the name of the medical device serviced;**
2. **any device identification(s) and control number(s) used;**
3. **the date of service;**
4. **the individual(s) servicing the device;**
5. **the service performed; and**
6. **the test and inspection data.**

Each manufacturer should analyze the service reports they receive directly, as well as the ones they receive from contractors, using the appropriate statistical methodology referenced in 820.100. It is important that this service data be collected and organized such that it can be analyzed to determine if quality problems exist. See Chapter 15, Complaints, for more details. If the report represents an event which is reportable to FDA under medical device reporting (MDR) requirements in 21 CFR part 803 or 804, these reports shall be handled as complaints using 820.198.

Contract agreements between the manufacturer and contractors and/or consultants will vary in their degree of complexity. The most comprehensive is probably the agreement between the manufacturer and the contract sterilizer. Thus, the contract sterilization agreement is an excellent

example of what is involved in setting up a contract between the device manufacturer and a contractor. The steps necessary for an agreement may be less extensive with other contracts than it is with the sterilization contract; however, the sterilization contract does provide a good basis for understanding this contractual agreement.

CONTRACT STERILIZATION

Manufacturers of medical devices frequently use contract sterilizers to provide sterilization processing for their devices prior to distribution. Contract sterilization of medical devices shall be performed so that the device manufacturer and the contract sterilizer meet the applicable parts of both the QS regulation and the labeling requirements of 21 CFR 801.

Labeling Requirements

Manufacturers of sterile devices commonly label devices as sterile at one establishment and ship them to another facility or to a contract sterilizer for sterilization. Shipments of nonsterile devices labeled as sterile are clearly misbranded and adulterated, and they may be diverted into consumer channels, thus creating a health hazard. FDA recognizes that this longstanding practice is an economic necessity for many manufacturers. Therefore, to meet the needs of these manufacturers in a way that will also assure the protection of the public health, FDA added Part 801.150(e) to the Code of Federal Regulations (CFR). This part identifies the necessary markings for such shipments and requires a written agreement which specifies the sterilization process. Part 801.150(e) It is reprinted below:

(e) As it is a common industry practice to manufacture and/or assemble, package, and fully label a device as sterile at one establishment and then ship such device in interstate commerce to another establishment or to a contract sterilizer for sterilization, the Food and Drug Administration will initiate no regulatory action against the device as misbranded or adulterated when the nonsterile device is labeled sterile, provided all the following conditions are met:

(1) There is in effect a written agreement which:

(i) Contains the names and post office addresses of the manufacturers involved and is signed by the person authorizing such shipment and the operator or person in charge of the establishment receiving the devices for sterilization.

(ii) Provides instructions for maintaining proper records or otherwise accounting for the number of units in each shipment to insure that the number of units shipped is the same as the number received and sterilized.

(iii) Acknowledges that the device is nonsterile and is being shipped for further processing, and

(iv) States in detail the sterilization process, the gaseous mixture or other media, the equipment, and the testing method or quality controls to be used by the contract sterilizer to assure that the device will be brought into full compliance with the Federal Food, Drug and Cosmetic Act.

(2) Each pallet, carton, or other designated unit is conspicuously marked to show its nonsterile nature when it is introduced into and is moving in interstate commerce, and while it is being held prior to sterilization. Following sterilization, and until such time as it is established that the device is sterile and can be released from quarantine, each pallet, carton, or other designated unit is conspicuously marked to show that it has not been released from quarantine, e.g., "sterilized awaiting test results" or an equivalent designation.

Quality System Requirements for Contract Sterilization

The sterilization process are performed in compliance with applicable parts of the Quality System regulation for medical devices because sterilization is a manufacturing process. Thus, the contract sterilizer is a manufacturer [(820.3(o)] and the device master record (DMR) shall contain, or refer to, the location of sterilization process specifications. Process specifications may be generated by either the manufacturer, contract sterilizer, or by both parties, although overall responsibility rests with the finished device manufacturer. The device manufacturer is ultimately responsible for assuring that its devices are sterile. The responsibility for specific tasks may be delegated to a contract sterilizer, but the device manufacturer retains the ultimate responsibility. The contract sterilizer is subject to those parts of the QS regulations that apply to the operations that it performs for the finished device manufacturers, e.g., equipment maintenance and calibration, in-process controls, and associated record keeping, etc. Thus, both the manufacturer and the contract sterilizer share the responsibility to comply with the QS regulation in assuring effective sterilization.

Because the responsibility for effective sterilization is shared between the device manufacturer and the contract sterilizer, it is essential that the two parties clearly define in writing the division of responsibility for every aspect of the sterilization process. The QS arrangements between the manufacturer and the contract sterilizer may be in the same written agreement used to cover the 801.150(e) labeling requirements. It is the manufacturer's and contractor's responsibility to assure the agreement is a workable practical document and is followed by both parties. FDA inspects finished device manufacturers and contract sterilizers to determine compliance. The following is QS related information that should be in the written agreement for contract sterilization and implemented during production, sterilization, and release.

Information Transfer

The manufacturer and contract sterilizer should designate the individual(s) at each facility responsible for coordinating the flow of information between establishments and for approving changes in procedures. All technical, procedural, and other information that pertains to the sterilization process and associated activities should pass through these designees. The manufacturer and the contractor shall agree to inform one another of any device or process changes, especially those that may require cycle requalification.

Record Keeping

Documentation such as device master record procedures, device history records, etc., to be used and maintained should be specified. If changes are made to the documentation, both parties should

agree on the manner in which the changes are to be made. These documentation changes shall comply with QS requirements in 820.70(b) and .75(c) for manufacturing and process specification changes, and with 820.40(b) for changes in device master records.

Process Validation

The device manufacturer has primary responsibility for the validation of the process used to sterilize its devices. Commonly, responsibility for portions of the validation study are delegated to the contract sterilizer in the written agreement. The manufacturer should work with the contract sterilizer to assure that the facilities, equipment and processing parameters (including preconditioning and aeration steps) will provide for effective sterilization and will not adversely affect the devices or their packaging. Validation is required for every device or device family. The written agreement should identify responsibility for all aspects of validation and define the criteria, frequency, and responsibility for requalification. Likewise, the agreement should identify the documentation that is maintained for validation studies.

Bioindicators and Dosimeters

The agreement should specify responsibility for placement, retrieval, handling, and processing of product samples and any biological, chemical, or physical indicators. The agreement should include instructions for packaging and shipment of indicators and samples to test laboratories for analysis.

Loading Configuration

The loading parameters for each lot of device(s) or device family should be specified. The routine product load configuration should conform to the validated load configuration. It is not recommended that a contract sterilizer mix products from different manufacturers in processing cycles unless validation studies have proven the effectiveness of the cycle for those mixes or worst case mixes, and the customers are informed about the practice.

Preconditioning

The agreement should address preconditioning requirements for external preconditioning and/or in-chamber conditioning if required by the sterilization process.

Cycle Parameters and Process Control

The written agreement should specify the cycle parameters to be achieved during processing. After the process is qualified, the contract sterilizer is responsible for maintaining control over the process to make certain that process specifications are routinely achieved. Cycle parameters should be clearly defined in written specifications, accurately monitored, and the actual parameter values achieved during each run should be recorded.

The primary manufacturer should produce the product under a quality system, which includes appropriate environmental control procedures such as bioburden control. Thus, the product is the "same" product as that for which the original process was developed or specified.

Post-sterilization Handling and Aeration

The agreement should address procedures for post-sterilization quarantine of the product before release for distribution. While waiting for release, the pallets, cartons, or designated unit shall be marked to indicate the status of the product; for example, "sterilized: awaiting test results," or an equivalent statement. If an aeration period is required, it should be specified. Both parties should acknowledge that the product is not to be shipped for commercial distribution until it is properly approved for distribution in accordance with procedures in the agreement.

If correctly labeled, a device that has been sterilized may be shipped to a controlled distribution point before final release by the manufacturer. Routine distributors are NOT considered to be "controlled distribution points." Shipments to a company warehouse or to another finished device manufacturer may be acceptable as long as the manufacturers are able to show that they have control of the product until final release and could recall it if necessary. See CFR 801 Subparts A & E and QS sections 820.160, Distribution, and 820.80(d), Final Acceptance Activities.

History Records and Review

Both the manufacturer and contractor should agree on the procedures and responsibility for reviewing and approving the device history records.

Finished Device Release

The agreement should include device release procedures. Individuals responsible for approving device release for distribution should be identified. A contract sterilizer may handle the final release of a batch of sterilized devices. The manufacturer should make sure, however, that this agreement is part of a written contract. In addition, the manufacturer should: audit or have a consultant audit the contract sterilizer; review the contractor's own QA audit report; or obtain written certification of compliance to assure that personnel and procedures are adequate to meet the requirements of 820.160, Distribution, and, 820.80(d), Final Acceptance Activities.

Audits of Both Facilities

The device manufacturer should audit his quality system and assure by audits or other means such as a review of the contractor's own QA audit that the contractor has adequate control over the sterilization process. The agreement should cover the extent and frequency of the audit, corrective actions, records, confidentiality, and the auditor(s).

Training

The manufacturer should assure that the entire sterilization process is performed and controlled by properly trained operators. The agreement should provide the manufacturer access to applicable training
records during agreed upon audits.

Nonconformance

Both parties should mutually agree to inform one another if the device or process deviates from the agreed upon specifications. As appropriate, the nonconformance should be investigated, evaluated, and, if necessary, corrective actions should be instituted. The parties should consider and agree on conditions requiring corrective action and document all reprocessing. The agreement should specify the individuals that should be contracted regarding any changes or deviations in the manufacturing or sterilization process. It should also specify the individual at the manufacturer that should be contacted when product is damaged to determine how the product should be handled at the contract sterilizer.

It is highly recommended that manufacturers of sterile medical devices read Sterile Medical Devices-A GMP Workshop Manual. This publication may be obtained from National Technical Information Services (NTIS), phone: 703-487-4650. The ordering number is: PB84188713. As of 7/96 the price is $71.50 for a paper copy and $12.50 for a microfiche copy.

FINISHED DEVICE EVALUATION

Finished device inspection is typically a final test and review of safety, performance, labeling, appearance, and configuration characteristics to assure the device meets the acceptance criteria established in the DMR. For many medical devices this assurance requires an analysis, electrical test, mechanical test, or other technical tests. For some simple devices, however, such as eyeglass frames, a visual or dimensional check may be sufficient to prove acceptability. For both simple and complex devices the manufacturer shall have written specifications or criteria for determining the acceptability of the finished device. It is important that the device characteristics to be evaluated are defined and also, where applicable, the equipment, environment, and handling procedure should be defined and established.

Sampling Plans

To show the manufacturing process is operating in a state-of-control, the process may need to be validated as explained in chapter 4, Process Validation. Testing product by using a sampling plan based upon an acceptable statistical rationale may demonstrate that the process continues to operate in a state of control. A manufacturer should be prepared to demonstrate the statistical rationale for any sampling plan used. Plans should be developed by qualified mathematicians or be selected from established standards such as ANSI Z1.4. Copies of this standard may be obtained by writing to: American National Standards Institute, 11 West 42nd Street, 13th Floor, New York City, NY 10036, or phone 212-642-4900.

All sampling plans have a built-in sampling risk of shipping devices that do not meet product specifications. Each sampling plan can be graphically illustrated to show the relationship between: the quality of lots submitted for sampling inspection and the probability that the sampling plan will yield a decision to ship the lot. ANSI Z1.4 contains operating characteristic curves for sampling plans presented in them. These curves can be used to determine the risk each sampling plan presents.

When sampling plans are used, there exists the possibility that a few defective devices will be shipped to the user. Thus, manufacturers should be aware of the risks a particular plan presents to the manufacturer and to the user. Questions such as those listed below should be considered before selecting a sampling plan.

- **Will the defect be obvious to the user? If not, what are the consequences of using the defective device?**
- **What is the state-of-the-art technology for 100% valid testing of this device?**
- **Is the testing destructive?**
- **Does the competition use sampling?**
- **What is the probability of a product liability suit?**
- **What are the regulatory consequences?**
- **Does the marketplace expect or accept devices that have been sample tested and/or inspected?**

Manufacturers should recognize that straightforward logical answers to these questions may not always be suitable. Acceptance status for devices may be influenced by the price the user is willing to pay -- 100 percent testing usually costs more than sampling. Destructive testing makes 100 percent testing impossible. Whether sample testing and inspection of a particular family of devices is acceptable to the user also changes with technology. Where 100% valid automatic testing is not feasible, validation of the process and the product with a follow up sampling plan is usually the preferred method of establishing and maintaining a quality system, which can continuously produce a device that meets specifications.

Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that it meets its current approved specifications. Rework and reevaluation activities, including a determination of any adverse effect from the rework upon the product, shall be documented in the device history record (DHR) [820.90(b)(2)].

When a device fails testing, it should not be repeatedly retested until it passes. The problem should be corrected. If a manufacturer's acceptance procedures allow acceptance after repeated testing and rework, there should be a valid basis for such an acceptance procedure. Failed devices shall be identified and segregated from acceptable devices and from the flow of the production process.

Labeling and Packaging Inspection

The manufacturer shall establish and maintain procedures to control labeling. This control includes the label's integrity, inspection, storage, control numbers, and labeling related operations (820.120).

The manufacturer shall control labeling and packaging operations to prevent labeling mixups. The label and labeling used for each production unit, lot, or batch shall be documented in the DHR [820.120(d)]. Where a control number is required by 820.65, that control number shall be on, or

shall accompany, the device through distribution [820.120(e)]. The DHR shall include or refer to the location of the primary identification label and labeling used for each production unit [820.184(e)].

The manufacturer shall ensure that the device packaging and shipping containers are designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution (820.130, Device Packaging). This may include containers and packaging examination as applicable to assure they are not damaged or misbranded. All devices shall have the correct labels, package inserts, and/or manuals as specified in the DMR.

Records

A DHR is a compilation of records containing the production history of a finished device [820.3(i)]. However, procedures for establishing and maintaining DHR shall be developed. These records demonstrate the device is manufactured in accordance with the DMR. The DHR shall include or note the location [820.80(e), 820.184] of:

- **dates of manufacture;**
- **quantity manufactured;**
- **quantity released for distribution;**
- **acceptance records demonstrating the device is manufactured in accordance with the DMR;**
  - **- date of acceptance**
  - **- results of acceptance activities**
  - **- signature of person(s) performing acceptance activities**
  - **- where appropriate, equipment used**
- **primary identification label and labeling used for each production unit; and**
- **any device identification(s) and control number(s) used.**

The DHR should be reviewed before distribution because these records are used to show that finished devices are manufactured in accordance with, and meet, the specifications in the DMR.

Beside these requirements, some device manufacturers should fulfill an additional traceability requirement if their device is intended for surgical implant into the body or to support or sustain life and whose failure to perform when properly used in accordance with the label instructions for use can be reasonably expected to result in a significant injury to the user. For these devices procedures shall be established and maintained to identify a control number for each unit, lot, or batch of finished devices and, where appropriate, components. The control number is used to trace a defective lot and facilitate corrective action. Identification of devices shall be documented in the DHR (820.65).

Product Release

Finished device manufacturers shall have sufficient controls to assure that only devices that have passed test and inspection are released as discussed in chapter 14, Storage, Distribution and Installation. The manufacturer shall establish and maintain procedures for identifying product during all stages of receipt, production, distribution, and installation to prevent mixups (820.60). Each manufacturer shall establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria. To prevent mixups, not-yet-accepted and rejected devices shall be controlled to prevent mix up with devices that have been through final evaluation and accepted for release [820.80(d)]. Methods of controlling non-releasable product include storage location, boxing, or manifest tagging. The desired end result is to assure operations are in a state-of-control. Finished devices should not be released for distribution until:

- **the activities required in the manufacturers DMR are completed;**
- **the associated data and documentation are reviewed;**
- **the release is authorized by the signature of a designated individual(s); and**
- **the authorization is dated.**

EXHIBITS

Examples of forms that may be used for purchasing, accepting, receiving, and inspecting components are exhibited at the end of this chapter. These examples show the types of information required by the Quality System regulation. Procedures and forms for a particular situation may be more or less comprehensive than these, and may assume other formats or arrangements according to need.

Purchase of Components

This exhibit is a specification for purchasing a zener diode and is typical of device master record documents that are used to purchase components. This spec describes the diode in sufficient detail for the correct part to be procured.

Acceptance of Components

This example is intended as an acceptance procedure that may be followed by a small to medium size manufacturer. The procedure has space for the number, revision level, and a blank for "ECN History." The history blank is for adding brief notes about changes that have been made to this procedure. Included as part of this procedure is a "Receiving History Log" which immediately follows the procedure. The other forms mentioned in the procedure are not reprinted; however, similar forms are included with the "Procedure for Receiving and Inspection of Material" described below with the example located immediately following the "Receiving History Log."

Material Receiving and Inspection Procedure

This document is a more extensive receiving procedure than the one discussed above and it can be used by a medium to large manufacturer. As part of this procedure you will note an extensive revision record section. Also, part of the procedure is a flow chart which outlines the steps in the procedure and the branches for each step. Next is a "Daily Report of Goods Received" which includes the supplier name, quantity received, lot number or item number, purchase order or requisition number, and information on where the item was sent. The next item in the procedure is a "Receiving and Inspection Report" which contains information about the item and the sampling and testing performed on the item. The report includes an acceptance or rejection slot along with a space for the cause for rejection. The procedure continues with a "Daily Inspection Log" which is a summary of the items received and their disposition, either accepted or rejected. Finally, as part of the procedure, we find examples of the decals to be used to accept, reject, or quarantine the incoming items.

Identification Decals and Forms

Examples of decals and travelers used to identify materials, components and in-process assemblies are exhibited. Two of the decals deal with components and can be used as a means of assuring proper disposition of these items. A "Material Lot Identification" is exhibited which is used to identify components in a container. This form has space for, among other information, lot number, expiration date, quantity in the subject container, date it was issued to stock, and the person who received the container. The final example in this group is a "Stock Requisition" form,

used whenever items are being released from stock to production. This form contains information such as, part number, quantity ordered and issued, and lot number. Note that part of this form is used to indicate if the issued item is to replace a defective item.

Receiving Rejection Notice

This form is used when incoming components and materials are rejected and includes sections for the inspector's report listing the sampling plan, specification tested for, number of defects, and a description of the defects. There is a section for a preliminary review, if necessary, and finally a section for the Material Review Board (MRB) decision on the disposition of the rejected lot. A MRB may accept temporary deviations that do not affect safety and effectiveness. These deviations or changes should be approved by the MRB or other designee. MRB activities should be performed per a written procedure and otherwise meet GMP requirements. The MRB should not change a device master record (DMR) drawing or be used as a substitute for the primary change control system of a manufacturer.

TITLE: IN4278 ZENER DIODE SPECIFICATION NUMBER

Drafted by _____ **App.** _____ **Date** _____

REV.	ECN History	Date

1. SCOPE: This specification describes a one-watt zener diode used for voltage reference in the XYZ Stimulator.

2. ELECTRONIC CHARACTERISTICS

2.1 Zener Voltage: 3.1 vdc @ 76 madc

2.2 Maximum Zener Impedance: 10 ohms @ 76 madc

2.3 Reverse Leakage Current: (25%) 100 microamps (max) @ l vdc

3. TESTING: All diodes shall meet the requirements of JANTX IN4278 as specified in MIL-S-19500/127G.

4. PHYSICAL CHARACTERISTICS

4.1 Diodes shall be packaged in a void-free silicone case.

4.2 Leads shall be readily solder able.

5. MARKING

5.1 The cathode shall be identified by a color band.

5.2 An identification number and lot number or date code shall represent a specific manufacturing period.

5.3 All markings shall be permanent such that cleaning solutions will not remove the markings.

6. CERTIFICATION

6.1 A certification of compliance with this specification and a test data sheet must accompany each lot shipped.

6.2 Certification must include a statement that no changes have been made in materials or physical or electrical characteristics.

7. APPROVED SUPPLIERS

7.1 XXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXX

TITLE: ACCEPTANCE OF COMPONENTS **Sheet 1 of 3**

No. Rev. ECN History

Drafted by App. by Date

1.0 SCOPE

These procedures are to be followed in the receipt, inspection, and storage of product such as raw materials, components, parts, manufacturing materials, etc., used in the manufacture of the XYZ Stimulator, a device that does not require traceability per 820.65.

2.0 RECEIVING

2.1 All incoming shipments must be examined for external signs of damage. If the shipment is damaged, immediately notify Purchasing and move the shipment to the unloading Hold area until disposition is decided by Purchasing.

2.2 Upon receipt, check each shipment against the corresponding purchase order and verify identity and quantity. The purchase order may include, reference, or have attached purchase specifications.

2.3 Enter the appropriate data into the Received Goods Log for each shipment received.

2.4 After completing the data entry, attach a yellow "HOLD" tag to the product and immediately move the products to the receiving quarantine area. The pink copy of the purchase order must accompany the product.

2.5 Notify Quality Control when materials requiring inspection are received in the quarantine area. This information is obtained from the device master record specification for the item ordered.

2.6 Quality control shall, after examining the product for damage and identity, move the product, etc., to be inspected to the Receiving Inspection area.

3.0 INSPECTION

3.1 Pull the inspection history file for the product to be inspected. This file contains the Receiving History form and inspection procedure. Enter the appropriate data from the purchase order onto the Receiving History form and perform the inspection per the procedure.

3.2 The QC manager shall assign a five digit lot number to each supplier lot received and enter the number on the Receiving History form.

3.3 After the inspection is completed, enter on the Receiving History form:
- **a. the quantity accepted and sent to stock;**
- **b. the quantity rejected; and**
- **c. your signature and the date.**

4.0 DISPOSITION

4.1 Receiving and test data for each shipment are sent to the designated individual for review and the decision regarding the acceptability of the lot.

4.2 For accepted product, enter the quantity accepted, date accepted, and lot number on a green "ACCEPTED" tag, attach the tag to the product, etc., and move it the stockroom.

4.3 For rejected product attach a red "REJECTED" tag to the rejected product and complete a Rejected Material form. Place all rejected product in the rejected quarantine area and forward the Rejected Material form to Quality Engineering for disposition.

5.0 STOCKROOM

5.1 All items entering the stockroom must be accompanied by a green "ACCEPTED" tag.

5.2 Components and other materials shall be stored and issued per SOP 17320.

5.3 Components and other materials will be issued from the stockroom on a first-in, first-out basis. All materials with a limited shelf life or requiring controlled storage conditions will be stored appropriately per SOP 17321.

Note: Sheet 3 is the Receiving History log for this procedure. The other forms mentioned in this procedure are not reprinted. However, similar forms are included with another procedure located later in this chapter.

RECEIVING HISTORY RECORD

Description

Purchase Order #	Lot #	Date Rec'd	Supplier	Lot Size	Quantity Accepted	Quantity Rejected	Inspect Date	Comments

DRAFT BY _____ **NUMBER PA-1004**

APPROVED _____ **SHEET 1 OF 9**

TITLE **PROCEDURES FOR RECEIVING AND INSPECTION OF MATERIALS (Receiving and Inspection Report Procedures (R.I.R)**

PURPOSE **This procedure outlines the activities and responsibilities involved in the receipt and inspect purchased product.**

SCOPE **This procedure applies to the receipt and initial evaluation of incoming components, material other product; preparation of the receiving and inspection report; quarantining of received item the inspection and accept/rejection of items.**

CONTENTS

REVISION RECORD

REV.	DESCRIPTION	ORIGINATOR	Q.A	OPER. MANAGER
A	ORIGINAL ISSUE			
B	REVISED			

1.0 PROCEDURES FOR RECEIVING AND INSPECTION

1.1 Responsibilities of Receiving Clerk.

1.1.1 Sign for items received.

1.1.2 Verify numbers of packages, check for obvious shipping damage and verify identification of packages to bill of lading.

1.1.3 Record information in receiving log and assign sequential receiving number.

1.1.4 Obtain packing slip from container of items.

A. Attach to bill of lading, if available.

B. Stamp receiving date on package slip.

C. Obtain receiving copy of purchase order from file.

D. Verify count, hidden damage and identification of items to packing slip.

If there is a problem, refer information to supervisor for resolution.

E. Circle quantity on packing slip.

F. Record receiving number on packing slip.

1.1.5 Production items.

A. Prepare part 1 of the receiving and inspection report (RIR). Use receiving number as RIR number.

B. Record receiving number on yellow quarantined tag and attach to item.

C. Move parts to quarantine area.

D. Send RIR to inspection.

E. Send packing slip to purchasing.

1.1.6 Non production items.

A. Send packing slip to purchasing.

B. Move material as per purchase order.

1.2 RESPONSIBILITIES OF RECEIVING INSPECTION

1.2.1 Receive RIR.

1.2.2 Obtain parts from quarantine area.

1.2.3 Obtain necessary instruction documents, such as specification sheets and purchase orders from Q.C. files and uncontrolled drawings from engineering files.

1.2.4 Perform inspection in accordance with instructions.

1.2.5 Record results of inspection on part II of RIR, sign, and date.

1.2.6 Fill out inspection log.

1.2.7 File original of RIR by receiving number.

1.2.8 If incoming materials are accepted:

A. Prepare green approval tag and attach tag to container, or item as appropriate.

B. Destroy yellow quarantine tag.

C. Return parts to quarantine area.

D. Discard pink copy of RIR.

E. Send yellow copy of RIR to material handler.

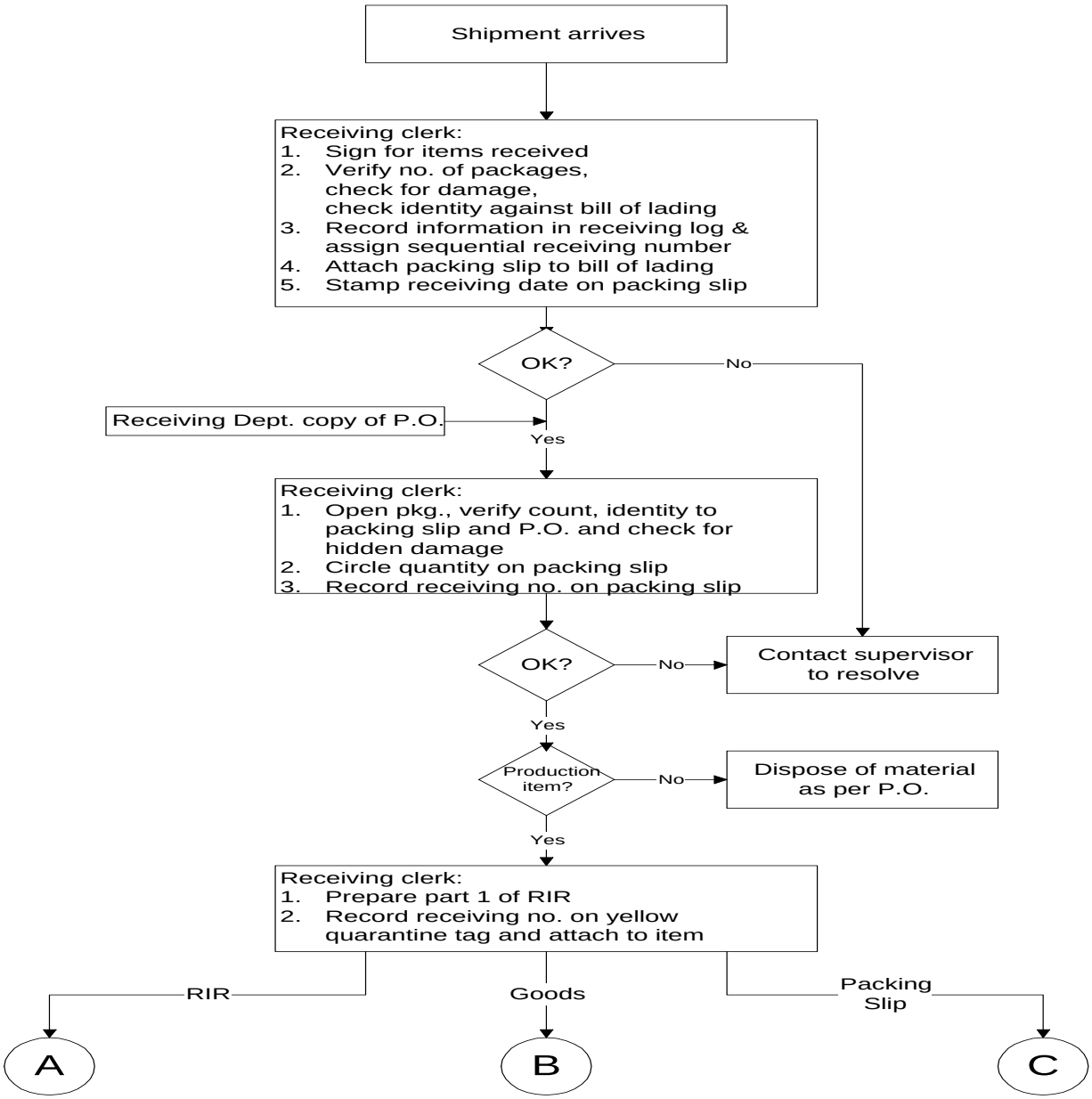
1.2.9 If incoming materials are non-conforming:

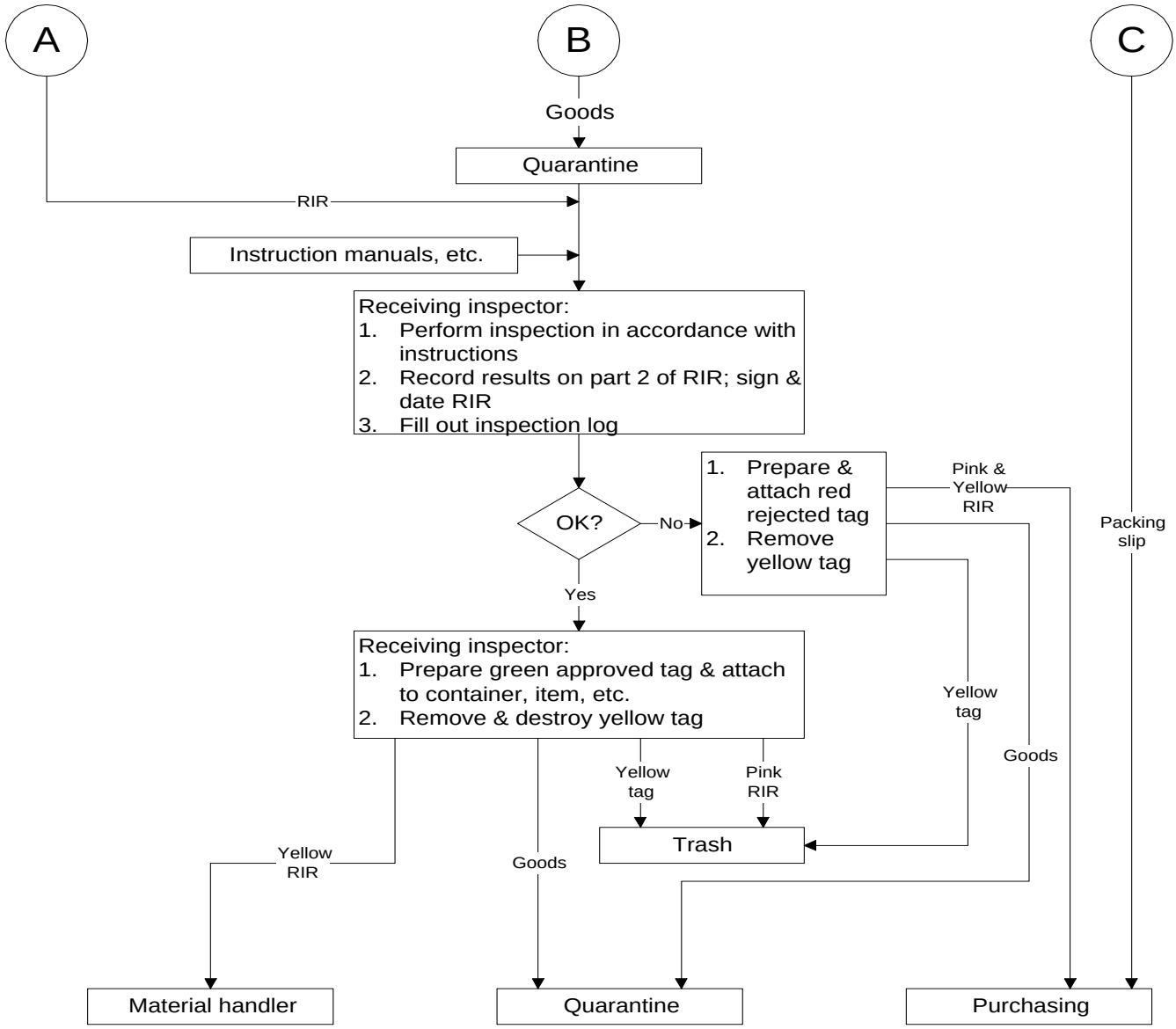
A. Prepare red rejection tag and attach to container, or item, as appropriate.

B. Destroy yellow quarantine tag

C. Return parts to quarantine area.

D. Send pink and yellow copies of RIR to purchasing.


Shipment arrives
Receiving clerk:
1. Sign for items received
2. Verify no. of packages,
check for damage,
check identity against bill of lading
3. Record information in receiving log &
assign sequential receiving number
4. Attach packing slip to bill of lading
5. Stamp receiving date on packing slip
OK?
No
Receiving Dept. copy of P.O.
Yes
Receiving clerk:
1. Open pkg., verify count, identity to
packing slip and P.O. and check for
hidden damage
2. Circle quantity on packing slip
3. Record receiving no. on packing slip
OK?
No
Contact supervisor
to resolve
Yes
Production
item?
No
Dispose of material
as per P.O.
Yes
Receiving clerk:
1. Prepare part 1 of RIR
2. Record receiving no. on yellow
quarantine tag and attach to item
RIR
Goods
Packing
Slip
A
B
C


A
B
C
Goods
Quarantine
RIR
Instruction manuals, etc.
Receiving inspector:
1. Perform inspection in accordance with instructions
2. Record results on part 2 of RIR; sign & date RIR
3. Fill out inspection log
OK?
No
1. Prepare & attach red rejected tag
2. Remove yellow tag
Pink & Yellow RIR
Packing slip
Yes
Receiving inspector:
1. Prepare green approved tag & attach to container, item, etc.
2. Remove & destroy yellow tag
Yellow tag
Goods
Yellow tag
Pink RIR
Trash
Yellow RIR
Goods
Material handler
Quarantine
Purchasing

Receiving Clerk _____ **Date** _____ **Sheet No. 6 of 9**

Received From	Via	No. Pkgs.	Weight	Quantity	Description of Goods	P.O. OR Req. No.	Charge Paid	Delivered to

Remarks:

RECEIVING & INSPECTION REPORT

No. A

PART I - RECEIVING

SUPPLIER: _____ **P.O. NO:** _____ **Date:** _____

Qty. Rec'd. _____ **Part No.** _____ **Spec. No.** _____

Description _____

Remarks _____

PART II - INSPECTION **Inspected by** _____

Sample Lot **Conformance to Specifications**

		YES	NO		YES	NO
Lot Size _____	**Physical Damage**	___	___	**Electrical**	___	___
Sample Qty. ____	**Markings**	___	___	**Dimensions**	___	___

Accepted _____ **Date** _____ **Rejected** _____ **Date** _____

Place in Stock **Cause for Rejection** _____

Forward to Next Operation _____

_____

_____

PART III PURCHASING

Rejected Parts Disposition **Conditional Acceptance Approvals**

Return to Supplier_____ **Remarks: Mfg.** ___ **Eng.** _____ **Q.C.** _____

Comments:_____

_____

_

DAILY INSPECTION LOG

DATE	RIR NUMBER	ACC-REJ REJ/ACC S/D	DATE	RIR NUMBER	ACC-REJ REG/ACC S/D	COMMENTS SPECIAL DISPOSITION

QUARANTINED	**RIR**

APPROVED			**RIR**
Product or Material			
Part or Spec #	**Quantity**	**Author**	**Date**
Remarks			

REJECTED			
By Quality Control			
Product or Material			
Part or Spec #	**Quantity**	**Author**	**Date**
Remarks			

MATERIAL LOT IDENTIFICATION

PART NO. _____ **REV.**____

DESC. _____

LOT CONTROL NO. _____

EXPIRATION DATE _____

QTY. THIS CONTAINER _____

DATE TO STOCK _____ **RECEIVED BY**__

CAUTION

TRACEABLE COMPONENT

MUST BE ISSUED BY LOT NUMBER ! RECORD LOT NUMBERS ON ISSUING DOCUMENT !

CAUTION

TRACEABLE COMPONENT

Part No. _____
Desc. _____
Lot Control # _____
Quantity _____

STOCK REQUISITION

For Dept. _____ **Date** _____

Is this material for: **[ ] Replacement of Defective Mat'l** **[ ] Bulk Issue** **[ ] Sales Order No.**____
N.O.D. # _____ **[ ] Test Inv.**
[ ] Kit Error **[ ] ECN No.** _____ **[ ] Other**

-

PART NUMBER	BIN CTRL	Posted	ORDER QTY.	ISSUED QTY.	BACK ORDER QTY.	LOT CONTROL NUMBER

IF STOCK-OUT ITEMS TO BE BACK ORDERED CHECK BOX [ ]

FILLED BY _____

REQUISITIONER_____ **PRODUCTION CONTROL APPR'L** _____ **DATE** _____

No _____

RECEIVING REJECTION NOTICE

VENDER NAME			PART NUMBER	
			PART NAME	
			P.O. NUMBER	QUANTITY RECEIVED
DATE RECEIVED	RECEIVING NUMBER	DATE INSPECTED	INSPECTOR	CROSS/REF.

INSPECTOR'S REPORT

ITEM	SPECIFICATION	SAMPLE PLAN			NUMBER OF DEFECTS FOUND	DESCRIPTION OF DEFECTS
		AQL	SAMPLE SIZE	ALLOW DEF		

PRELIMINARY REVIEW

CHECK	DISPOSITION	EXPLANATION
	RETURN TO SUPPLIER	
	USE AS IS	
	MATERIAL REVIEW BOARD	
	OTHER	

Q.C.	DATE	M.C.	DATE	PURCHASING	DATE

MRB DISPOSITION

CHECK	DISPOSITION OF LOT	ITEMS INVOLVED	AMOUNTS INVOLVED	MRB AUTHORIZATION		
				MRB	SIGNATURE	DATE
	REJECTED RETURN TO SUPPLIER FOR REPAIR OR REPLACEMENT			Q.C.		
	USE AS RECEIVED PER LIMITATIONS LISTED ON D.E.O			ENG.		
	USE AS RECEIVED. SEE LIMITATIONS LISTED UNDER COMMENTS			OTHER		
	ACCEPT PENDING SPECIFICATION CHANGE PER E.O.					
	SCREEN AND/OR REWORK BY PURCHASING NOTIFY SUPPLIER OF COST					
	OTHER (SPECIFY BELOW UNDER COMMENTS)					

COMMENTS _____

Acceptance for future shipments will depend on proper completion and return of this report by supplier within 14 days to

CAUSE OF DISCREPANCY	CORRECTIVE ACTION TAKEN

EFFECTIVE DATE	SIGNATURE & TITLE	DATE

11 LABELING

LABELING REGULATIONS

Medical devices in commercial distribution in the U.S. shall be properly labeled according to laws and regulations enforced by the Food and Drug Administration (FDA). Specific labeling requirements for medical devices are contained in:

- **The Federal Food, Drug, and Cosmetic (FD&C) Act;**
- **The Fair Packaging and Labeling Act;**

- **The Radiation Control for Health and Safety Act;**

- **Title 21 of the U.S. Code of Federal Regulations, Part 801 for general devices, and Part 809 for in vitro diagnostic products;**

- **Title 21 of the U.S. Code of Federal Regulations, Part 812.5 for investigational devices;**

- **Title 21 of the U.S. Code of Federal Regulations, Part 820 for design and manufacturing controls for labeling; and**

- **Title 21 of the U.S. Code of Federal Regulations, Part 1010 - Performance standards for electronic products. Also see Parts 1020 and 1040.**

Section 201(k) of the FD&C Act defines the term "label" as "a display of written, printed, or graphic matter upon the immediate container of any article . . . ." Under Section 201(l) of the FD and C Act, the term "immediate container" does not include a package liner. Any word, statement, or other information appearing on the immediate container should also appear on the outside container or wrapper, if any, of the retail package or be easily legible through the outside container or wrapper. The label is not required to appear on the shipping carton.

Section 201(m) of the FD&C Act defines the term "labeling" as all labels and other written, printed, or graphic matter: (1) on the device or any of its containers or wrappers, or (2) accompanying the device. The term applies any time while the article is in interstate commerce, or being held for sale after shipment or delivery in interstate commerce. The term "accompanied" is interpreted liberally. It extends to posters, tags, pamphlets, circulars, booklets, direction sheets, fillers, etc., that may be displayed in proximity to the article or shipped to the user before or after shipment of the device.

The distinction between labeling and advertising, while both draw attention to the article to be sold, is often nebulous or superficial. Both are forms of publicity and are used for an identical purpose. An appellate court described the relationship between the two as follows: "Most, if not all, labeling is advertising. The term 'labeling' is defined in the Act [section 201(m)] as including all printed matter accompanying any article. Congress did not, and we cannot, exclude from this definition printed matter which constitutes advertising."

Section 502(f)(1) and (2) of the FD&C Act requires that device labeling bear adequate directions for use, operating and servicing instructions, and either adequate warnings against uses dangerous to health, or information necessary for the protection of users. All devices require directions for use unless specifically exempted by regulation. Conditions for exemption from this requirement are in 21 CFR 801, Subpart D.

Misbranding

Section 502 of the FD&C Act contains the misbranding provisions for drugs and devices. It states a device is misbranded under a number of different circumstances, including:

- **Its labeling is false or misleading.**

- **Its packaging does not bear a label containing the name and place of business of the manufacturer, packer, or distributor, and an accurate statement of the quantity of contents.**

- **Words, statements, or other required information are not prominent on the labeling or are not stated clearly.**

- **It is intended for human use, and the label fails to bear the name and quantity or proportion of any narcotic or habit-forming substance contained in the product, and fails to display the statement, "Warning: may be habit forming."**

- **Its label does not contain adequate directions for use. These include warnings against use in certain pathological conditions; against use by children where its use may be dangerous to health; and against unsafe dosage, methods, duration of administration or application unless exempt as unnecessary to protect the public health.**

- **It is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling.**

- **It does not comply with the color additive provisions listed under Section 706 of the FD&C Act.**

The Medical Device Amendments expanded the authority of the FD&C Act over misbranded medical devices. These amendments contain further circumstances under which a device is misbranded:

- **The device's established name (if it has one), name in an official compendium, or including common or usual name, is not printed prominently in type at least half as large as used for any proprietary name.**

- **The device is subject to a performance standard and it does not bear the labeling requirements prescribed in that standard.**

- **There is a failure or refusal to comply with any requirement prescribed under Section 518 on notification and other remedies; failure to furnish material or information requested by or under Section 518; or failure to furnish any materials or information requested by or under Section 519 on records and reports.**

- **The device is commercially distributed without FDA concurrence on a 510(k) premarket notification submission.**

False or Misleading Labeling

Section 502(a) states that a drug or device is misbranded if its labeling proves false or misleading in any particular. It is not a necessary condition that the labeling should be flatly and blatantly false for the FDA to take action. The word "misleading" in the FD&C Act means that labeling is deceptive if it creates or leads to a false impression in the mind of a reader. A "false impression" may result not only from a false or deceptive statement, but may be instilled in the mind of the purchaser by ambiguity and indirection. It might be caused by failure to inform the consumer of facts that are relevant to those statements actually made. In other words, the label that remains silent as to certain consequences may be as deceptive as the label that contains extravagant claims. Examples of misleading labeling include: ambiguity; half truths; trade puffery; expressions of opinion or subjective statements; and failure to reveal material facts, consequences that may result from use, or the existence of difference of opinion.

In the past, labeling found by the agency to be objectionable has featured such practices as: deceptive pictorial matter; misleading testimonials; misleading lists of parts or components; and brand or trade names instead of "established names" (see Sections 201(h), 502(e)(2), and 508 of the FD&C Act). Examples of false representations are:

- **incorrect, inadequate or incomplete identification;**
- **unsubstantiated claims of therapeutic value;**
- **inaccuracies concerning condition, state, treatment, size, shape, or style;**
- **substitution of parts or material;**
- **subjective or unsubstantiated quality or performance claims; and,**
- **use of the prefix U.S. or other similar indication suggesting government or agency approval or endorsement of the product.**

Adequate Directions for Use

Title 21, CFR Part 801.5, defines "adequate directions for use" as "directions under which the layman can use a device safely and for the purpose for which it is intended." See Part 801.4 for a definition of "intended use."

Among other reasons, directions for use may be inadequate because there is partial or total omission or incorrect specification of one or more of the following items:

- **Statement of all conditions, purposes, or uses for which the device is intended. This includes conditions, purposes, or uses for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising. This statement also includes conditions, purposes, or uses for which the drug or device is commonly used. These statements should not refer to conditions, uses, or purposes for which the drug or device can be used safely only under the supervision of a practitioner licensed by law; those conditions, uses, and purposes may only be referred to in advertisements directed to a licensed practitioner.**
- **Quantity of dose including usual quantities for each intended use and usual quantities for persons of different ages and physical conditions.**
- **Frequency of administration or application.**
- **Duration of administration or application.**
- **Time of administration or application in relation to meals, onset of symptoms, or other time factors.**
- **Preparation for use, adjustment of temperature, or other manipulation or process.**

Prescription Devices

Labeling exemptions for prescription devices are in 21 CFR Part 801.109. These are devices which

because of a potential for harmful effect, potential for misuse, or the collateral measures necessary to use, are not safe except under the supervision of a practitioner licensed by law. Hence "adequate directions for use" cannot be prepared for these devices. They are exempt from Section 502(f)(1) of the FD&C Act provided that all conditions specified in the labeling regulation are met.

These conditions state that the device shall be in the possession of a person, or his or her agents, or employees regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale distribution of prescription devices; or in the possession of a practitioner such as a physician, dentist, or veterinarian licensed by law to use or order the use of these devices. These devices can be sold only to, on the prescription of, or by order of such practitioner for use in the course of their professional practice.

The label of the prescription device, other than surgical instruments, is required to bear:

- **the statement "Caution: Federal law restricts this device to sale by or on the order of a _____", the blank to be filled with the word "physician", "dentist", "veterinarian", or with the descriptive designation of any other practitioner licensed by the law of the State in which he or she practices to use or order the use of the device; and**

- **the method for its application or use.**

Labeling on or within the package from which the device is to be dispensed shall also bear information for use under which practitioners licensed by law to administer the device can use the device safely and for the purposes for which it is advertised or represented. This labeling information includes indications, effects, dosages, routes, methods, frequency, and duration. Safety labeling includes relevant information on hazards, contraindications, side effects, and precautions.

When a device is capable of producing serious injury, even when used by a person thoroughly familiar with its operation, the directions for use shall provide detailed information. FDA has specific regulations on the labeling of intrauterine contraceptive devices, 21 CFR 801.427, and for diagnostic x-ray devices, 21 CFR 1020.30(h). In addition, FDA has issued general guidances for labeling certain devices, i.e., transcutaneous electrical nerve stimulators and electronic muscle simulators.

Where appropriate, directions for use should be supplemented with adequate warnings against the use of the drug or device under certain conditions. Any caution statement, similar to the directions statement, may appear in the labeling of the product; it is not necessary that it be printed on the label. In each instance, the responsibility for the adequacy of the warning statement appearing on the labeling rests with the manufacturer or distributor. For some devices, there are national consensus standards that specify that certain caution statements be on the device. There is no list of prescription devices in the CFR.

Sterile Devices

Special attention should be given to the labeling of sterile devices. For example, sterility may be needed only for a portion of certain devices and this condition should clearly be identified in the labeling. Devices that are not sterile in their entirety should be labeled to properly inform users what is actually intended to be "sterile" in the package. For example, a possible limiting statement might be:

"Caution: Only the fluid path of this set is sterile and nonpyrogenic. Do not use in a sterile or aseptic area without proper precautions."

The label of multi-device kits or packages containing a combination of sterile and nonsterile products will be considered to be false or misleading if it implies that all contents are sterile.

Some devices are intended to be sterilized by the user before use. In this situation, the labeling should provide adequate information about a suitable method of sterilization and any precautions or safeguards to be followed. For example, the labeling should describe any:

- **special cleaning methods required;**
- **changes in the physical characteristics of the device that may result from reprocessing which affect its safety, effectiveness, or performance; and**
- **limit on the number of times resterilization and reuse can be done without affecting the safety or effectiveness of the device.**

In the case of single-use sterile devices, many manufacturers include labeling to advise against resterilization and reuse. Some devices are not designed or constructed to be recleaned, and may not be capable of withstanding the necessary recleaning and resterilization procedures. Where reuse is common practice, manufacturers are encouraged to provide the information described in the above list.

The need for users to have instructions on how to open a sterile device package to avoid contamination of the device also needs to be evaluated. When necessary, such instructions should be included in the labeling.

If a manufacturer modifies a device, the manufacturer should also review the labeling to ensure that it reflects current revisions and specifications. Thus, change control forms should contain a check off box for labeling and packaging. Some manufacturers identify labeling with a drawing number plus a revision code or date as an aid in identifying current labeling. The package insert or other labeling for in vitro diagnostic products is required to contain the revision date [21 CFR 809.10(b)(15)].

Shelf-life dating solely for package integrity and sterility is not usually required for general medical devices. There may be a need for expiration dating when a particular component of a device, such as a battery or diagnostic reagent, has a finite useful life. Labeling for in vitro diagnostic devices [809.10 (a) and (b)] requires an expiration date or some other means by which users may be assured of quality at the time of use. This requirement applies to both sterile and nonsterile in vitro diagnostic devices.

Although not required by regulation, most manufacturers of complex devices and sterile devices voluntarily use lot or serial numbers for production control and, if the need arises, to expedite failure investigations, repairs, modifications, or recalls. Lot, batch, or other control numbers are required for:

- **implantable and life sustaining devices [820.65, Traceability];**
- **some products subject to radiological health standards [1002.30(b)(1), Records to be maintained by manufacturers]; and**

- **in vitro diagnostic devices [809.10(a)(9), Labeling for in vitro diagnostic products].**

DESIGN OF LABELING

Various sections of the Quality System (QS) regulation have an impact on labeling including: section 820.30, Design controls; section 820.80, Receiving, in-process, and finished device acceptance; and section 820.70(f), Production and Process controls, which requires buildings to be of suitable design and have sufficient space for packaging and labeling operations. Section 820.120 deals with specific requirements for device labeling. These sections apply controls to the labeling content to meet the needs of the user and patient, as well as to meet the labeling specifications contained in the device master record. Applying the regulations to the physical design applications of labeling assures legibility under normal conditions of use over the expected life of the device. It also helps assure the proper inspection, handling, storage, and distribution of labeling. The requirements in 820.30(c), Design input, address the intended use of the device, and the needs of the user and patient.

Labeling includes equipment labels, control labels, package labels, directions for use, maintenance manuals, etc. The displays on CRTs and other electronic message panels are considered labeling if instructions, prompts, cautions, or parameter identification information are given.

Adequate labeling for a medical device requires proper design and procurement of the labels and labeling. Design includes generating the content of labels and labeling and making sure the content meets FDA requirements as well as the needs of the customer. To achieve these goals a number of concepts must be kept in mind such as: writing to the reader, referring to the actual device in labeling, obvious identification of the controls used, etc. Design controls for label integrity are discussed later.

There are some basic guidances, rules, and practices that can be used to immediately improve writing. The following paragraphs will discuss them, with emphasis on how they can be used to make labeling clear and comprehensible.

As an essential aid, writers are encouraged to obtain a copy of *40,000 Words* published by Webster's New World Dictionary or a similarly titled book by any of the reference-book publishing companies. Most of these reference books have about four pages of punctuation rules. Using these pages of rules can immediately improve not only the style and clarity but also the accuracy of your writing. Writers are also encouraged to obtain and use a standard college-level text on technical writing.

Write to the Reader

The most serious problem is that writers tend to write to themselves. Their material is clear to them so they mistakenly think it is as clear to others. For example, the sensitivity control on an instrument is called "gain" control on page one of the instruction manual, "amplitude" control on page two, and "level" control in the next section. Further, the photograph in the introduction shows the same control with a call-out identification note labeled "Signal Adjust." No wonder readers get confused! Yet the author of the example knew what he was trying to write about and, most certainly, he was writing to himself.

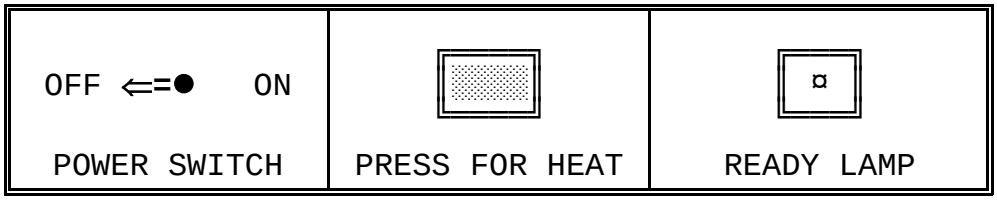
When writing labeling, especially for an over-the-counter (OTC) device, the author must know the reading level of the target audience. If data on reading levels is not available, this may necessitate reader interviews to establish a reading level for the target audience. If the device is designed for home use, a useful guide is *Write It Right* available through DSMA.

Refer to Actual Device

One simple way to reduce control identity confusion as described above, reduce other types of labeling errors, and increase clarity is for authors to keep a labeled instrument, kit, or photograph(s) nearby and refer to it as they write. It is easier to write the truth when you know the truth. Make sure the terminology and descriptions in the labeling match that on the actual device. It is best to always use the same title for each given item or control throughout the manual, insert, label, and advertisement. Likewise, the same title should be used in charts, figures, or screen displays such as cathode-ray tubes, LCD panels, etc. Remember to write to your intended readers, write with a labeled device or photographs in sight, and use consistent titles.

Obvious Identification of Controls

Because the title of controls or other items in screen displays and other labeling should be exactly the same as in the labels on equipment, reagents, accessories, etc., authors may need to develop and use an appropriate correlation technique for corresponding titles in instruction manuals, package inserts, etc. One common and simple technique is to use all capitals for the titles of controls in labeling. For example:



The associated text, for example, might state:

Flip the POWER SWITCH to ON.
In about three seconds, the READY LAMP will illuminate.
Now press the HEAT button to switch the heater on.

With this correlation technique, the words "on" and "off" are capitalized in the labeling only when they actually appear on the instrument control panel. Note that "ON" is capitalized in "POWER switch to ON" as the actual switch has "POWER," "ON," and "OFF" printed by it. In contrast, note that "on" is not capitalized in the statement "to switch the heater on" as it is not a label of a control on the device. Also, be careful to use a simple correlation system that is readily apparent to the intended audience.

Don't Distract Reader

Readers are very busy trying to learn how to use a new device. They should not be annoyed by any unnecessary distractions such as:

- **changes in format,**
- **unusual typeface,**
- **incorrect page numbers, and**

- **incorrect figure numbers.**

For a person trying to read in a hurry, a font such as script can be a major distraction; therefore, it is best not to use script, italics, or any other unusual or hard-to-read type-faces. Remember, you have decided to write for the benefit of the intended audience. Forget about your personal preferences and use only the most common fonts. Also, select a type size that is readable at the intended distance. For example, labeling displayed on the screen of a wall-mounted heart monitor should be readable from several feet away. Also, use a consistent format throughout the document. Check the format and section titles against information on the contents page. In some cases, such as for in vitro diagnostic products, the arrangement of information in the labeling may be dictated by a regulation. Page numbers should not be referenced in instruction or service manuals. It is too easy for the actual page numbers to be changed during the original writing or when the manual is updated. It is much better to refer to paragraph titles or numbers as these are less likely to change; and, if changed, titles are more noticeable by writers and typists than are page numbers. The use of correct figure numbers is easy -- just check them.

Short and to the Point

It is important to use sentence structure that will convey the intended message with a minimum of misinterpretation or need to reread. Tests have been conducted to determine the ability of readers to follow instructions in a sentence based on the number of activities to be performed. The average person's ability to follow instructions decreases rapidly when a sentence contains more than two facts. (Keep in mind your own experiences in reading instructions.) Therefore, sentences in labeling need to be short and to the point. Avoid long strings of adjectives and be specific. Try to be as specific as possible with your instructions. For example, "ambient" or "room temperature" generally should not be used. Instead specify the desired or necessary range of operating conditions. In many cases a list of activities to be performed is better than burying the facts in long sentences. A numbered list is better if the user may have to repeat any part of the procedure. If it takes lots of words to get to the point, the reader will probably miss the point! Short, choppy sentences are acceptable in instruction manuals and other labeling. You are not trying to entertain readers with beautiful, flowing prose -- rather, you want to catch their attention with key facts so they correctly perform the specified instructions. Thus, use short sentences, get to the point, be specific, and keep graphics and pictures near the corresponding text.

Gobbledygook

Another way to be more specific and shorten sentences is to avoid "gobbledygook." The following terms were collected from actual instruction manuals:

ORIGINAL	PREFERRED EQUIVALENT
Makes provisions for	*
Serves to	*
At the time of	When
In conjunction with	And
Carried out in	Perform
Comes up to	Reaches
Will also serve as a chance to	May
Will be sure that will	Ensure
Available through the use of	*
Care should be used so as not to	Be careful

Be provided for positive determination	*****
Causes power to be applied to	**Switches power to**
Due to the fact that	**Because**
Take the form of	**Be**

In most cases, the equivalent term in the list can replace the original term. For the asterisked items, the equivalent is simply a direct statement of what is intended. Of the terms listed, the combination most often used is "makes provision for." Simply eliminating "makes provision for" and "be provided for" from labeling will result in an immediate improvement for readers.

Introduce Each Item

Always introduce each control, indicator, device, or subject before it is discussed in the text. The introductions should be brief and may be very brief. Keep in mind the items will be described in more detail later. Abbreviations and new or uncommon terms should be defined. The introductions and definitions prevent readers from going into mental shock, breaking their train of thought, and asking: What is this? By then readers have probably forgotten the last two or three facts read. Also, readers may wonder about any "cliff-hanging" item when they resume reading. This disturbance may detract readers from fully assimilating the next instructions being read. To avoid distractions and confusion, a writer of labeling should always:

- **introduce each item, and**
- **define new or uncommon terms.**

With respect to definitions, a writer should never give a new meaning to an existing common term in the language. To avoid this disservice, coin a special term or code number such as Class Q, Code 1, or Level 2.

Accentuate Key Terms

Whenever it is stated in instructions that something shall be done, then "shall" should be set in bold type, or otherwise delineated. Likewise, caution and warning statements should be emphasized by boxing, bold type, etc. Underlining should not be used as it makes the descending part of a letter hard to read and appears to be top lining on some printers. Refer to any regulations or standards for a specific product and use the recommended or required caution statements. When standard terminology exists in a consensus standard, creating new caution statements is not advisable. Confusion is less likely to occur when one stays with the commonly understood terminology.

Select Words Wisely

When large print is needed for reading at a distance or to attract attention to signs, caution labels, and screen prompts, words generally should be short in order to fit the available space. This rule also applies to the wording on control labels. This situation places a burden on the writer to select terms that convey the desired message. Consider the following wording from two actual highway signs:

PLANT TRAFFIC	**NO FISHING**
ENTERING HIGHWAY	**OFF BRIDGE**

Have you ever been run over by a pachysandra? If you can't fish off the bridge, does that mean you are allowed to fish only on or from the bridge? Better choices for the intended messages are: "Traffic entering highway" and "No fishing from bridge".

Test Labeling

Finally, always have someone not familiar with the product operate it exactly according to the draft instructions, labels, screen displays, etc. You should not do any coaching because coaching destroys the validity of the trial. By coaching you transfer your "memory" to the user. Therefore, no coaching -- this is the "acid" test -- good luck! During the trials, note any significant problems and make appropriate corrections to the instructions, prompts, or other labeling.

Label Integrity

All labels shall be designed and applied to devices and containers so that the labels will remain in place and legible during the customary conditions of distribution, storage, and use [820.120(a)]. Likewise, other labeling such as user instructions should remain legible during customary storage and use. For example, labeling printed by machines onto plastic in vitro diagnostic media plates is often smeared and thus is inadequate [FD&C 502(f)]. The manufacturers of such devices should assure that the print is legible and will remain legible until used.

Many magazines use "wet" ink which smears when touched by sweaty or oily fingers. Obviously, this type of ink will not meet the design requirements for package inserts, instruction manuals, and the like.

Labels may be mounted by adhesives, screws, rivets, drive screws, etc., or printed or etched onto panels and/or onto controls. The labels should be located so that they will be seen but not be abraded during use. (Many of us have seen the unbelievable cases where safety labels on ladders and riding lawnmowers were placed in the foot rest areas. Of course, they were worn off after a few uses!)

Approval Policy and Procedure

The review of labeling from the design stage through to the finished device should be documented like the review of other significant components. This includes the labeling development, any changes, and final approval. Documentation should be included in the design history file of the procedures used, signature of the responsible person, and date. Because several activities are performed and controlled during the development and use of labeling, Table 11.1, "Drafting and Approval of Labeling" and "Final Approval of Labeling, Advertising, Etc." are presented as guidances. This table contains a typical sequence of events required to develop and control labeling. Other controls are discussed below.

Before release for use, labeling should be reviewed and approved by product development, service, marketing, quality assurance, and other appropriate managers (820.30). Manufacturers need to have a policy/procedure which covers the drafting, review, and approval of labeling. Approval forms are generally used in conjunction with such a policy/procedure. A sample approval form and procedure are presented at the end of this chapter. Other procedures and forms such as

"Change Control" are referenced in this procedure. Note that this procedure also covers other elements such as a correct device master record, correct transfer of labels into production, lot control, change control, etc. Samples of various procedures appear at the end of chapters throughout this manual.

Design Transfer

Specifications are required in the device master record for the content and physical design parameters of labels. (see Chapter 8). Labeling specifications include the engineering drawing and/or artwork for each label, appropriate inspection or control procedures, and appropriate procedures for attaching the labels. All procedures, drawings and artwork should have the name of the preparer, an approval signature, and a date. The approval signature, date, etc., may be on the back side of artwork or on a label approval form. Further, artwork may contain only an identification code or title if the "content" of the artwork is duplicated on approved engineering drawings, adequately identified, or cross-referenced with respect to the label approval form. That is, a manufacturer should be able to identify isolated artwork.

Hardcopy labels, package inserts, and similar labeling are also specified and purchased as components (see Chapter 8). For correct purchase and use of labeling, specifications are usually stated on engineering drawings and/or purchase specifications. Thus, artwork or "copy" alone will not fulfill the device master record and purchasing control requirements for labeling except for the most simplistic labeling such as brief errata sheets.

The engineering drawings or purchase specifications should specify, as appropriate, the label substrate, dimensions, ink, finish, mounting method, etc., so that the purchased label will remain attached and legible during the customary conditions of processing, storage, handling, distribution, and use.

Table 11.1 TYPICAL SEQUENCE OF THE CONTROL OF LABELS

PHASE	SECTION	CONTROL ACTIVITY
1. Design	820.30, 820.120 & 820.130	Meets needs of user and intended use. Text review. Quality of mounting such as rivets, adhesives, etc. Quality of ink, anodize, etc. Content per 21 CFR 801 and 809 company claims and standards.
2. Verification/ Validation	820.120, 820.75 & 820.30	Simulated or actual processing such as sterilization, shipping tests, label affixing, etc. Saline, alcohol, and coffee spill tests?
3. Changes	820.30 & 820.75	Establish and maintain approval procedures.
4. Documentation	820.30, 820.181 & 820.120(e)	Approve, date and change control label drawings. A key label shall contain the control number of the finished device either on or accompanying device.
5. Procurement	820.120(b) 820.180	Proofread before release to inventory stock. Record signature of proofreader and date.
6. Storage	820.120(c) & (d)	Store labels to prevent mix-ups. Restrict access to authorized persons.
7. Separate operations	820.120(d)	Separate multiple operations to prevent mix-ups.
8. Area	820.120(d)	Before beginning labeling operations, designee to inspect area and remove

inspection		**extraneous devices and labels.**
9. Issuance	**820.120(b), 820.120(e) & 820.65**	**Examine for identity and, where appropriate, expiration date and control number. Record date and person examining labels.**
10. File Sample	**820.184(e)**	**Copy of primary identification label shall be in the device history record.**
11. Inspection	**820.80(d), 820.86 & 820.80(e)**	**Inspect finished device per written procedure. Designee shall check all acceptance records and test results and see that requirements are met and records are present and complete.**

Front panels, other instrument panels, meters, fuses, pushbuttons, and the like often are either labels or contain labels and thus should, as appropriate, meet device master record and control requirements. Component specifications, assembly drawings, and test/inspection procedures are appropriate controls to prevent mixup of meters, push buttons, and other labeled instrument controls.

Whether a manufacturer considers a software driven display to be labeling or data makes little difference under the QS regulation because, either way, the finished device labeling or data should meet the device master record specifications. When manufacturers develop and validate software, they should also review any electronic displays to see that the "labeling" meets all applicable requirements, such as adherence to specifications in the device master record, correct parameter identification, agreement with the instruction manual, and, of course, correct display of performance data.

Production Controls

When reviewing or auditing labeling operations, it is wise to keep in mind that the GMP requirements are flexible. The degree of labeling control needed to satisfy the QS regulation varies considerably for different devices and operations. In order to avoid wasting money and increasing the cost of health care, manufacturers need to give considerable and prudent thought to the appropriate level of control needed for their operations as allowed by 820.5. Information and guidances presented in this manual should aid manufacturers in making these decisions. The level of control needed should be reconsidered when products are changed. Likewise, the controls needed, and the success of the existing control program, should be reviewed during quality system audits (see Chapter 17).

Medical device manufacturers should incorporate in their quality system several elements that relate to labeling in order to meet the GMP requirements. The quality system should be adequate to assure that labeling reflects user needs, meets the device master record requirements with respect to legibility, adhesion, etc., and assure that labeling operations are controlled so that the correct labeling is always issued and used.

Receipt and Inspection

Upon receipt, all packaging and labeling materials, including preprinted containers, inserts, and preprinted packaging materials, should be examined and, if deemed necessary by the company, tested to assure conformance with specifications as discussed in Chapter 10, Purchasing and Acceptance Activities. Also, samples of labels, including labeled panels, meters, etc., shall be proofread by a designated individual(s). After being accepted by a responsible individual, these components may be placed into inventory or into production. These inspections shall be recorded in

the device history record as required by 820.80(e) and 820.120(b) to show that inspection and proofreading were performed. The inspection record for device labeling should be kept simple.

Area Separation and Inspection

All labeling and packaging operations should be separated to the degree necessary [820.120(d)] to assure there are no mixups between similar products or labels. Separation may be either a physical or spatial separation or by performing the labeling and packaging at different times for different devices. Separation is not required when mixups are impossible, such as the case of labeled front panels that only fit the intended family of devices.

The likelihood of a labeling mixup determines how stringent production area controls should be. For example, label control need not be stringent if only one product or dissimilar products and labeling that are unlikely to create confusion are processed. Before beginning any packaging and labeling operation in which mixups could occur, the production area and equipment for the operation should be thoroughly examined to ensure that any devices and labeling materials remaining from previous operations have been removed. It is important to make certain that the surrounding area, tables, packaging lines, printing machines, and other equipment are cleared of labels and other materials used in the previous operation.

Unused labeling that contains pre-coded serial numbers, manufacturing dates, expiration dates, control numbers, etc., should be destroyed and not returned to the label storage area. The GMP requirements do not include reconciliation of the number of labels used with the number issued, although, this control is recommended for some devices, such as when different sizes of the same product are being packaged or otherwise labeled.

STORAGE

Where feasible, labels for similar devices should be designed with different shapes and colors to reduce the probability of mixups. Thereafter, all printed packaging and labeling materials, including preprinted containers, inserts, and preprinted packaging materials shall be stored in an area and manner suitable to prevent mixups [820.120(c)]. For example, if labels from one container are accidentally dropped, they should be stored so they will not fall into another container of similar labels. Labeling should be identified and segregated to the degree necessary to prevent mixing of similar labeling. Access to labeling should be limited to authorized personnel.

Storage control should be appropriate for the number and kind of devices. For example a manufacturer that has only one product with one label does not need an elaborately controlled storage area. Similarly, a manufacturer with only a few types of devices having dissimilar labeling would not normally require stringent control.

One case that requires dedicated attention to storage and control is prelabeled "sterile" but not-yet-sterilized devices. Manufacturers should make absolutely certain that mixups cannot occur. Also, they should make certain that all samples used for market promotion are sterile or labeled with a manifest caution statement, because a packaged and labeled market-promotion sample might be used by the recipient. One approach is to sell sterile samples at zero cost so that such samples are subjected to all of the company product release and distribution controls. Quality awareness training is required by section 820.25. Marketing personnel should be informed of labeling control requirements and the consequences of a violation.

Label Check and Record

In summary labeling should be carefully examined to assure that the contents of the labeling comply with the labeling specifications in the device master record. This examination should include any control numbers or expiration dates used on the labels. A record of this check, including the date and name of the person performing the examination, should be made in the device history record.

If expiration dates are used, they should reflect the time limitations within which the device is fit for its intended use when stored and used per its labeling. The manufacturer should have stability test data establishing how long the device will remain fit for use to support expiration dates.

If label mixups cannot occur -- for example, a manufacturer makes only one device or uses only one label -- and there are no control numbers or expiration dates, the original inspection when the labeling was placed into inventory is an adequate check for compliance with the device master record specifications. A second check need not be performed because it serves no purpose (820.5). If, however, there is any possibility that incorrect labeling can be used, a second check should be made when the labeling is issued for application, packaging, or shipping.

Control Numbers

Devices intended for surgical implant, and devices intended to support or sustain life and whose failure to perform properly can be expected to result in significant injury, shall contain a control number, serial number, letters, etc., for traceability (820.65). Procedures for establishing and maintaining control numbers shall be documented in the DHR. This means a control number for the finished device, and not the label itself. Although this control number may be on a label, most labeling also contains another number, such as a drawing number, for control of labeling configuration and procurement.

The control number for traceability need not be on every label on the device; however, the control number should appear on the primary label that goes to the ultimate user. The label on a shipping carton does not meet this requirement because bulk items may go to a central distribution point in the user-facility and the shipping carton will most likely be disregarded.

Access Restriction

Access to labeling should be restricted to authorized personnel. Labeling also should be stored in an adequately segregated area to minimize the chance of mixups. Segregation is recommended because it increases the control over the label storage area with no significant increase in cost.

CHANGES

Labeling is a component of the device and part of the device design output; therefore, all changes to labeling should be made under a formal change control system. Design changes shall meet 820.30(i); and other changes are made according to 820.40. Any changes to labeling should be formally reviewed and authorized before implementation. That is, follow the guidance in this chapter as if new labeling is under development.

When making changes to primary aspects of a device and to primary documentation, the review group should determine if any secondary items such as labels or instructions are affected and also need changing. There should be a check-off block on change-order forms, or any other change control mechanism, for recording that the effect of the primary change on labeling was considered

and appropriate action was taken. The failure of a change control system to alert employees of basic requirements is considered to be a serious deficiency in a quality system.

SHIPPING FOR PROCESSING

Devices that are prelabeled "sterile," but are not yet sterilized, require be controlled at the manufacturer and during shipment for further processing. Likewise, devices that have been sterilized and shipped to the manufacturer's warehouse or other controlled distribution point before final release should be properly labeled. The pallets, or designated unit, should be marked to indicate the status of the device, such as "non-sterile," "sterilized: awaiting test results," or an equivalent statement (820.86). The company should be able to show that it has control of the devices until final release and, could have them destroyed or returned for reprocessing if necessary. Unless so qualified, a distributor's warehouse or facility is not considered a controlled distribution point.

The QS regulation states that each manufacturer shall establish and maintain procedures to ensure that mixups, damage, deterioration, contamination, or other adverse effects to product do not occur during handling (820.140).

The storage regulation at 820.150 states, "(a) Each manufacturer shall establish and maintain procedures for the control of storage areas and stock rooms for product to prevent mixups, damage, deterioration, contamination, or other adverse effects pending use or distribution and to ensure that no obsolete, rejected, or deteriorated product is used or distributed. When the quality of product deteriorates over time, it shall be stored in a manner to facilitate proper stock rotation, and its condition shall be assessed as appropriate. (b) Each manufacturer shall establish and maintain procedures that describe the methods for authorizing receipt from and dispatch to storage areas and stock rooms."

Manufacturers of sterile devices commonly label devices as sterile at one establishment and ship them to another facility or a contract sterilizer for sterilization. Shipments of nonsterile devices labeled as sterile are clearly misbranded and adulterated, and if diverted into consumer channels, could create a potential health hazard. FDA recognizes that this longstanding practice is an economic necessity for many manufacturers. Therefore, to meet the needs of these manufacturers in a way that will also assure the protection of the public health, FDA added Part 801.150(e) to the Code of Federal Regulations (CFR). It is reprinted below.

> **(e) As it is a common industry practice to manufacture and/or assemble, package, and fully label a device as sterile at one establishment and then ship such device in interstate commerce to another establishment or to a contract sterilizer for sterilization, the Food and Drug Administration will initiate no regulatory action against the device as misbranded or adulterated when the nonsterile device is labeled sterile, provided all the following conditions are met:**

(1) There is in effect a written agreement which:

(i) Contains the names and post office addresses of the firms involved and is signed by the person authorizing such shipment and the operator or person in charge of the establishment receiving the devices for sterilization,

(ii) Provides instructions for maintaining proper records or otherwise accounting for the number of units in each shipment to insure that the number of units shipped is the same as the number received and sterilized,

(iii) Acknowledges that the device is nonsterile and is being shipped for further processing, and

(iv) States in detail the sterilization process, the gaseous mixture or other media, the equipment, and the testing method or quality controls to be used by the contract sterilizer to assure that the device will be brought into full compliance with the Federal Food, Drug and Cosmetic Act.

(2) Each pallet, carton, or other designated unit is conspicuously marked to show its nonsterile nature when it is introduced into and is moving in interstate commerce, and while it is being held prior to sterilization. Following sterilization, and until such time as it is established that the device is sterile and can be released from quarantine, each pallet, carton, or other designated unit is conspicuously marked to show that it has not been released from quarantine, e.g., "sterilized -- awaiting test results" or an equivalent designation.

OVER-LABELING

Over-labeling by placing a new label over an old label is discouraged by FDA but is acceptable as long as the new label and its use meet GMP requirements [(820.30, 820.120, 820.90(b)(2)] for user needs, attachment, legibility, reprocessing, and change control. Over-labeling is also discouraged in some foreign countries.

EXHIBITS

Exhibits that cover labeling design and labeling control are presented on the following pages. These exhibits show how some GMP requirements for label control may be met. These procedures and forms may need to be modified to meet the needs of a specific operation.

Drafting and Approval of Labeling

This drafting and approval procedure is used to establish a uniform system for controlling the content of labeling and for approving labeling. This procedure is adaptable for use by any size manufacturer. The approval form which follows may be used with this procedure.

Approval Form for Labeling, Advertising, Literature, etc.

This form is intended for use by a medium to large manufacturer, however, the checklist style can be adapted even to a small manufacturer. The areas of concern are listed under the group that is responsible for that concern. Thus, every department has input into the acceptability of the labeling.

Administration Set Label

This example of a label for an administration set begins with a complete description of the device inside the package. The directions for use section is arranged so that each point in the directions for use is numbered and only one point is made for each step. The various points in the directions are short and to the point. Where emphasis is needed, as in the case of air bubbles, the information is bolded for further emphasis.

Labeling Control Record

This blank copy of a labeling control record shows what a sample form looks like. At the bottom of the form, there is space to attach the actual labeling used so that a comparison of the actual labeling used versus that required can be made during product release review.

Device History Record: OB/GYN (Plate)

The history record exhibited here is limited to the filling operation for a media product. The form has space to print the same label as printed on the plates during the filling operation for label control and release review. This technique eliminates human copying errors.

User/Reader Comments

Feedback is an important element in any QA system. Whenever manuals or instructions form part of the labeling for a product, it is wise to solicit review from persons not familiar with the use of the product. These people can be employees of the manufacturer or, as in this exhibit, actual users of the product. The information received will reflect the problems encountered by persons trying to follow the instructions without any preconceived knowledge of the actual operation of the product.

Procedure Policy Title: DRAFTING AND APPROVAL OF LABELING SOP#:_____
Prepared by:_____App:_____Date:_____
Prep. Date:_____Rev:_____ Date:_____
ECN History: _____

1.0 PURPOSE

To establish a uniform procedure for controlling the content of labels and labeling and obtaining approval within our company.

To assure compliance with GMP requirements and with company policy directives.

2.0 SCOPE

Applies to all devices including those used for market research or clinical investigations.

Advertising material is excluded from this SOP. It is covered by our SOP #____, "Advertising Material Control and Approval."

3.0 REFERENCE DOCUMENTS

3.1 Food and Drug Administration LABELING, GMP, etc. requirements in 21 CFR Parts 800-1299.
3.2 SOP #_____, Advertising Material Control and Approval
3.3 SOP #_____, Change Control System

4.0 FORMS

4.1 Form SOP #_____, Labeling Development and Verification Checklist
4.2 Form SOP #_____, Labeling Approval Form
4.3 Form SOP #_____, Engineering Change Order Form

5.0 DEFINITIONS

5.1 Labeling is all labels and other written, printed or graphic matter accompanying or attached to the device or its container.

6.0 PROCEDURE

6.1 Preparation and Approval

The Labeling Development and Verification Checklist should be used as a guidance for all activities because the finished labeling must be evaluated versus this checklist.

6.1.1 The need for a label or labeling is determined by an operating department such as Engineering, Marketing, Manufacturing, or Quality Assurance. Marketing, as appropriate, will conduct and document literature searches and perform design input market research to determine any special needs of the users. Design input, regulatory, safety, and other appropriate information shall be used to create a labeling specification.

6.1.2 The Engineering Department prepares a manuscript complete with illustrations or prepares a drawing(s) of the label showing the wording, label use, and/or location. The label may be on a front panel drawing or other engineering drawing.

6.1.3 When final prototypes and/or pilot production models are available, the labeling shall be verified and the results recorded on the Labeling Development and Verification checklist. If needed, appropriate corrective action shall be taken by the appropriate department. The completed checklist shall be filed with the device design verification records.

6.1.4 Before final approval, labeling will be discussed at appropriate design review meetings. The minimum attendees are the originator, Engineering, and QA.

6.1.5 The Engineering Services Department then prepares form SOP #_____, Labeling Approval Form, and circulates it to the originating department, Training and Education, Marketing, and Quality Assurance for approval. (See the following sample approval form.)

6.1.6 Engineering Services will coordinate and file all labeling verification checklists, notes, approvals and approval forms in the design history file.

6.1.7 When approval is received from all parties, the label or manuscript is assigned a drawing number and is released and added to the product structure (DMR Index) following the Change Control System (SOP #_____) procedure.

6.2 Implementation and Control

6.2.1 When labels or labeling are produced, Quality Control must proofread the material and verify that it is correct by first article inspection and so indicate by signing an appropriate document.

6.2.2 All labels and labeling will be reviewed by QA for lot control requirements. Each original document will be marked by Engineering Services to indicate the level of control required. At least one label on each device intended for surgical implant into the body or to support or sustain life must have a lot, serial, or other control number. See 820.65, Traceability.

7.0 EXPERIMENTAL DEVICES

7.1 Labels and labeling for experimental or investigational devices are required.

7.2 The documentation need not be as complete as for production labels and labeling; but, it must be adequate to allow procurement of the labels or labeling and adequate for the intended use. If appropriate, such labeling must meet 21 CFR 812.5.

8.0 CHANGES

8.1 Any changes to released labels or labeling are accomplished according to SOP #_____, "Change Control System".

9.0 SCHEDULES

(Design QA requirements are presented below. There are also related production requirements.)

9.1 Drafts must be generated according to a schedule that allows a normal approval procedure. While urgent copy approval is occasionally necessary, it should not become standard operating procedure.

9.2 All labels must be approved according to the routine engineering schedule for components.

9.3 Labeling must be approved before or when the device is released for full-scale production. HOWEVER, any pilot units placed in commercial distribution must be labeled with approved pilot or final labeling.

9.4 The design review for any pilot lots and the design review of initial full-scale production lots shall include a design review of labeling.

9.5 The design review records for labeling shall be identified for easy recall. These records shall be a part of the design history file.

FINAL APPROVAL OF LABELING, ADVERTISING, Etc.
Return to Approval Coordinator after each signature or after checking any "no" box.
Title_____ Doc. No._____Dwg. No._____
Intended use/distribution _____
Project Leader _____
Approval Coordinator _____

Yes	No	N/Applicable	ENGINEERING
[]	[]	[]	Tech. specs., installation data, & part numbers correct.
[]	[]	[]	Procedural information is accurate and complete.
[]	[]	[]	Standards imposed by CSA, UL, IEC, etc. are met.
[]	[]	[]	Illustrations are technically accurate.
[]	[]	[]	Equipment protection cautions included where necessary.
[]	[]	[]	Procedures verified on final prototype or prod. model.
[]	[]	[]	Changes requested in draft have been made or negotiated.
[]	[]	[]	Procedures are safe and effective.
[]	[]	[]	Final draft has been proofread.

Project Engineer: _____Date: __/__/__
[]Approved []Approved with noted changes []Not approved
Engineering Services Mgr: _____Date: __/__/__
[]Approved []Approved with noted changes []Not approved

Yes	No	N/A	SERVICE
[]	[]	[]	Maintenance information is written for intended user.
[]	[]	[]	Lists part numbers needed for maintenance and repairs.

Service Manager: _____Date: __/__/__
[]Approved []Approved with noted changes []Not approved

Yes	No	N/A	TRAINING AND EDUCATION
[]	[]	[]	Document is adequate for training purposes.
[]	[]	[]	Document agrees with experience of training specialists, if experienced with this or similar products.

Training Manager: _____ Date: __/__/__
[]Approved []Approved with noted changes []Not approved

Yes	No	N/A	MARKETING
[]	[]	[]	Material is effective and complete for intended use.
[]	[]	[]	Material meets the needs of the international market.
[]	[]	[]	Material is professional and projects the company image.
[]	[]	[]	All claims supported by verification data.

Project Manager: _____Date: __/__/__
[]Approved []Approved with noted changes []Not approved
Director Marketing: _____Date: __/__/__
[]Approved []Approved with noted changes []Not approved

Yes	No	N/A	QUALITY ASSURANCE
[]	[]	[]	Hazards situations are highlighted with adequate warnings.
[]	[]	[]	All FDA labeling and GMP requirements, are met.

Quality Engineer:_____Date: __/__/__
[]Approved []Approved with noted changes []Not approved

Approval Coordinator _____ Date: _/_/
signature
Form # _____Approved _____Date: _/_/

MAJOR MEDICAL, INC.

ADMINISTRATION SET

Catalog Number 1403

With macro non-vented drip chamber, 80 inch length and "Y" site.

INSTRUCTIONS FOR USE

1. **Prepare solution container.**
2. **Close side clamp and open ____ device.**
3. **Remove protector cap from drip chamber piercing spike.**
4. **Aseptically insert spike through set port of solution containers.**
5. **Squeeze and release drip chamber until solution half fills the drip chamber.**
6. **Open slide clamp and allow the tubing to fill with solution, thus eliminating all air bubbles. DO NOT ALLOW AIR TO BE TRAPPED IN SET.**
7. **Close slide clamp.**
8. **Make venipuncture with I.V. device of choice.**
9. **Open slide clamp.**
10. **Regulate rate of infusion with ____ device.**
    Micro Set: 60 drops delivers about 1 ml; Macro Set: 15 drops delivers about 1 ml.
11. **To stop flow without disturbing valve adjustment, use slide clamp.**

PRECAUTIONS:

- **Supplementary medication may be injected with 20 or 22 gauge needle into injection site.**
- **If fluid path is interrupted, take special care to ensure fluid path has not been contaminated.**
- **Do not use to administer blood, blood products, suspensions, emulsions or any medication not totally soluble in the solution being administered. These medications may be administered through the distal Y-injection site with slide clamp closed.**
- **Puncturing drip chamber or tubing can cause air contamination and leaking.**

FOR SINGLE USE ONLY

CAUTION: Puncturing tubing can cause air embolism.

NONPYROGENIC
STERILE: Unless Package has been opened or damaged.
CAUTION: U.S.A. Federal law restricts this device to sale by or on the order of a physician.

STORE AT ROOM TEMPERATURE
Sterilized by E.T.O.
Date of Sterilization: _____
Lot No. _____

Manufactured for:
Major Medical, Inc.
Debbiville, Maryland 20906
Printed in U.S.A.

LABEL CONTROL RECORD

1. **Labeling area was inspected and no labels from previous operations were present.**

   Initials: _____

2. **Just before starting the labeling operation, labels were examined for correct:**

   [ ] Identity [ ] Expiration date on label [ ] Control number

   Name: _____ **Date:** _____

3. **REAGENT INFORMATION** **3.1. CONTAINER INFORMATION**

   Description _____ **Size** _____

   Catalog Number _____ **Type** _____

   Stability _____ **Quantity** _____

   Lot Number _____ **Other** _____

   Reagent Expiration Date _____ _____

   Initials _____ **Date Recorded** _____

4. **[ ] Labels were correctly applied.**

5. **[ ] Unused labels with filled-in expiration date were destroyed.**

6. **[ ] Remaining labels, if any, were returned to proper storage area.**

7. **Place sample(s) of labels here:**

8. **Inspector** _____ **Completion date** _____

Comments: _____

_____

9. [ ] Place completed form in the device history record for this lot.

I. INITIATION

DEVICE NAME: **OB/GYN** **THEORETICAL YIELD:** **2500**

DEVICE LOT NO.:_____ **EXPIRATION:**

INITIATED BY: _____ **DATE INITIATED:**

II. FILLING OPERATIONS

A. CONTAINER: **MFG:** **LOT NO.**

B. LABELING

LABEL PREPARED BY:_____

LABEL APPROVED BY: _____

. . . . . .
. .
. **Paste Label Here** .
. **or** .
. **Run This Sheet Through** .
. **Labeling Machine** .
. . . . . .

C. MEDIA

SECTION	MEDIA	BATCH NO.	TEMP. RANGE	DEPTH OF FILL (mm)
1	Levine EMB	_____	41-52 C	3.5 - 4
2	BiGGY	_____	41-52 C	3.5 - 4
3	Mannitol Salt Agar	_____	41-52 C	3.5 - 4
4	TSA w/5% Human Blood	_____	44-52 C	3 - 3.5
5	Mod. Thayer Martin	_____	44-52 C	2.5 - 3.5

FILLING ROOM PERSONNEL:

DATE DEVICES FILLED:

USER OR READER COMMENTS
In order to improve the quality and utility of our manuals and inserts, our company needs the active cooperation and participation of its user readership. Your comments as a user or reader will be greatly appreciated and reviewed for information in the next revision of this document.
Please comment on the completeness, accuracy, organization, usability, and readability of this manual or insert.
Did you find errors in this document? If so, specify by page.
How can this document be improved?
Other Comments:

User's Name:	**Position:**
Employer:	**Department:**
Address:	
City:	**State:**
Zip:	**Date:**
Country:	**Form Number: MKT-139 Rev. 1**

Revised: J. Strojny, 2-96
Edited: J. Puleo, 3-1
Revised: A. Lowery, 3-4

Edited: J. Strojny 3-4 and 3-12
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12 PRODUCT EVALUATION

INTRODUCTION

Product evaluation is performed to show with documented evidence that a component, in-process unit, or finished device was manufactured according to the device master record (DMR) and meets all of the acceptance criteria/acceptance specifications in the DMR. The blank forms for recording the data become a part of the DMR. The emphasis in this chapter is on finished device evaluation; however, evaluation of incoming product and in-process units is conducted according to the same type of controls [820.80(a), 820.80(b), 820.80(c)].

The GMP requirements for finished device evaluation are covered in section 820.80, which requires that the manufacturer establish and maintain procedures for finished device acceptance, to ensure that each production run, lot, or batch of finished devices meets acceptance criteria. Finished devices shall be held in quarantine or otherwise adequately controlled until released. Finished devices shall not be released for distribution until:

- **the activities required in the DMR are completed;**
- **the associated data and documentation is reviewed;**
- **the release is authorized by the signature of a designated individual(s); and**
- **the authorization is dated.**

Manufacturers shall also identify by suitable means the acceptance status of product, to indicate the conformance or nonconformance of these items with acceptance criteria. The identification of acceptance status shall be maintained throughout manufacturing, packaging, labeling, installation, and servicing of the product to ensure that only products which have passed the required acceptance activities are distributed, used, or installed (820.86).

If a manufacturer has adequate test and inspection procedures and these are used correctly by appropriately trained personnel, then there is a high probability that devices released for distribution will meet the company device specifications for acceptable product. Further, the data collected during in-process or finished device evaluation should be appropriate, complete, and

correct. This data shows the good and bad points about the product and specific production activities. The data may be fed back into the quality system to identify and solve real problems as well as to help maintain and improve the quality system.

Evaluation Specifications

In order to be assured that a device is fit for the intended use, a manufacturer should decide which characteristics of a device to test and/or inspect and to what detail or extent to test and/or inspect for conformance with the device specifications.

Decisions on what to test and how to test are made during the product and process development phase. For example, this decision is typically based on the:

- **intended use;**
- **intended user;**
- **nature of the device and its components;**
- **intrinsic safety of the device;**
- **reliability of the device;**
- **overall process capability of the manufacturing operation;**
- **characteristics of test and inspection equipment and procedures; and**
- **performance margin of the device compared to the device specification.**

Device test and/or inspection specifications, and test and/or inspection procedures, shall be carefully written and shall cover all appropriate points in the device acceptance specifications, in order to improve communication and reduce errors.

Design controls in 820.30(f) require device developers to verify the device design. Verification requires each manufacturer to write a test protocol and test, to the maximum feasible extent, all parameters of each device design against the design input specification. (The design input requirements become the input specifications at the verification stage of the development.) The verification test protocol includes the tests that will be performed on production units. Therefore, the production test procedures and some aspects of the inspection procedures are easily derived from the verification protocol.

Before the manufacturer is ready for full scale production, the test and inspection decisions shall be completed, documented as test/inspection or acceptance procedures, and approved for use. It is a violation of the FD&C Act to place inadequately evaluated devices into commercial distribution. It is also a violation of the quality system regulation to allow test and inspection procedures to evolve during production, except during a highly controlled pilot-production phase. Further, devices that are not adequately evaluated may not meet company written or unwritten quality claims -- manufacturers cannot bypass their responsibility by simply not writing quality claims. Under Section 501(c) of the FD&C Act, a device is adulterated if its purity or quality falls below that which it purports or is represented to possess.

By the time the manufacturer is ready for production, the device specifications shall be supported by one or more test and inspection procedures documentation. These procedures are part of the DMR. To reduce drafting, filing, retrieval, and copying costs, test and inspection procedures may appear on process and assembly documents. Combination documents are commonly used for the fabrication and inspection/testing of subassemblies. There may be several test and inspection

documents because evaluation may be performed at several in-process stages and at the finished device stage.

Although the manufacturer shall establish and maintain procedures for finished device acceptance, there are situations where a simple data sheet or blueprint may be referred to as the written acceptance criteria. For example, the acceptance of a simple molded or machined component or device may be determined by using a checklist, blueprint, or specification which specifies finished article dimensions, flash removal, etc. In machine-shop operations, a blueprint or engineering drawing may be used as acceptance criteria and used to meet the quality system written procedure requirements.

CORRECTIVE AND PREVENTIVE ACTION

GMP section 820.100 requires an analysis of problem data, returned product, and an investigation of non-conforming product. Also 820.198 requires an investigation of complaints that allege a device does not meet specifications. Section 820.100 refers to analysis of processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming or other quality problems. Section 820.198 also involves reviewing and evaluating complaints to determine whether or not an investigation is necessary. All these activities and their results shall be documented.

Some devices have a specified requirement for servicing. If this is the case, the manufacturer shall establish and maintain instructions and procedures for performing and verifying this servicing (820.200). The servicing reports shall also be analyzed using 820.100, Corrective and Preventive Action; if the servicing involves a death or serious injury, the service report is considered to be a complaint per section 820.198, Complaint Files, and is reported to FDA per parts 803 and 804, Medical Device Reporting.

The significance of the device and any hazard the defective device presents should be taken into consideration when determining compliance with corrective and preventive action requirements. Analysis shall be taken to the level necessary to determine the actual failure mechanism, e.g., defective component, incorrect raw material, erosion, composition, etc. The cause of failure is obvious in some cases and a formal investigation may not be needed. A record of the investigation, follow up, and conclusions shall be made in accordance with section 820.100.

When a systematic failure has been diagnosed, manufacturers need not analyze every device with the same diagnosed symptoms. However, enough devices should be analyzed to clearly establish symptoms before any assumptions are made about the cause of failure or about corrective actions. When an investigation results in identification of a deficiency, such as a failed component or a design flaw, and this deficiency may exist in other product lines, the investigation will not be effective unless it extends to determining the effect on other product lines.

If the failure is design related, the design shall be corrected per the design control requirements in 820.30 in order for the devices to meet company quality claims and not be adulterated under the FD&C Act section 501(c). When a failure is determined to be related to documentation, assembly, processing, labeling, testing, packaging, or other manufacturing operations, the manufacturing deficiency shall be identified, corrected, and documented.

REPACKER/RELABELER DEVICE EVALUATION

Finished devices received by a repacker/relabeler typically have been inspected and conform to specifications determined by the original manufacturer except for the final packaging and/or labeling. In most cases a repacker/relabeler would not have to assure that the finished device as received meets performance and configuration specifications. Finished bulk materials, such as dental resins, in vitro diagnostics, etc. may be accepted on the basis of a certificate of analysis for each batch.

Before releasing devices for distribution, repackers/relabelers should assure that devices are properly labeled (see chapter 11) and packaged (integrity, contents, etc., also see chapter 13). Often this can be accomplished using a list, illustration, or a model. When the packaged product will be sterilized or aseptically filled, written instructions and inspection/testing are necessary. Final acceptance of repacked/relabeled devices shall be recorded in accordance with 820.80(e). As noted, the final acceptance data is primarily related to correct labeling, correct packaging, and sealing of the packaging. In the case of aseptic filling operations, validation of the filling operations and finished device sterility testing are required.

NONCONFORMING PRODUCT

The manufacturer shall establish and maintain procedures to control product that does not conform to specified requirements. These established procedures shall include identification, documentation, evaluation, segregation, and disposition of nonconforming product. The evaluation of product non-conformance shall include a determination of the need for an investigation and notification of the persons or organizations responsible for the nonconformance. This evaluation and any investigation shall be documented (820.90). The manufacturer shall establish procedures for identifying the training needs of personnel who handle nonconforming products in the course of their work. These people should be trained to recognize product noncomformance and take appropriate action to control nonconforming products including identifying product as nonconforming, documenting and evaluating the nonconformance, and segregating and disposing of nonconforming product. This training should be documented (820.25).

To facilitate detection of failure or defect trends, internal problem data, including service reports, and complaints should be arranged in a way that permits correlating present and past data for a particular product or product line. This can usually be achieved by organizing files according to product or product lines. Such data may be maintained in a computer file for quick accessibility and analysis.

The manufacturer shall establish and maintain procedures that define the responsibility for review and the authority for the disposition of nonconforming product. Nonconformance may occur in-house, as well as before product is distributed, along with nonconformances of distributed product. Procedures shall set forth the review and disposition process. Disposition of nonconforming product shall be documented. This documentation shall include the justification for any use of nonconforming product and the signature of individual(s) authorizing this use [820.90(b)(1)]. The decision to use a nonconforming product is usually done by a material review board (MRB). MRB boards should operate according to a written procedure and be comprised of individuals having the knowledge to determine suitability for use of nonconforming product.

Each manufacturer shall establish and maintain procedures for rework, including retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications. Rework and reevaluation activities, including the determination of any adverse effects from the product rework, shall be documented in the DHR [820.90(b)(2)].

FAILURE INVESTIGATION

In order for a quality system to be self correcting, data on quality problems from all sources should be fed back into the system. For example, complaints, service reports, and nonconforming products can provide valuable information that can point toward possible corrective actions. The more comprehensive a quality system is in taking preventive action, the lower the probability of customer dissatisfaction and the resulting need for corrective action. A true quality system has many preventive safeguards including GMP requirements for design, packaging, labeling, manufacturing control, installation, repairs, and complaint and failure analysis. A quality system that also covers the customer needs generally results in increased overall quality and greater customer satisfaction.

Service requests resulting from long use, misuse or accidental damage usually do not require corrective and/or preventive action. However, if service requests or other customer concerns are the result of rapid wear, unusual problems, unusual maintenance, or development of hazardous conditions, action may be necessary.

The manufacturer shall establish and maintain procedures for implementing corrective and preventive action. The procedures shall include the following [820.100(a)]:

- **Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data. The purpose of the analysis is to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems.**

- **Investigating the cause(s) of nonconformities relating to product, processes, and the quality system.**

- **Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems.**

- **Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device.**

- **Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems.**

- **Ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems.**

- **Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.**

All these activities and their results shall be documented [820.100(b)].

EXHIBITS

Several forms for recording device production and evaluation data are briefly described below and then exhibited.

Portable Defibrillator Test Procedure

Ten pages extracted from a 31-page test specification for a family of portable defibrillators are reprinted below. This test procedure is long and detailed because a defibrillator is a complex device with a benefit to risk ratio that approaches infinity. This sample evaluation procedure covers final manufacturing, testing, and data collection performed by the production department to make absolutely certain that finished defibrillators comply with DMR specifications. This test procedure was developed based on the company approved device specifications.

To reduce errors and increase clarity, the test number column on the data sheet contains the paragraph number of the detailed requirements in the specifications section of the procedure. The test equipment and schematics are not reprinted here.

Test DHR of a Printed Circuit Board Assembly

A data or "device history record" card for a printed circuit board is exhibited. The test procedure for the board is not reprinted. This data card is not the complete device history record for the finished device. When the finished device is tested, this board is tested again as an integral part of it.

Device History Record (urine plate)

A record sheet of the filling, labeling sample, inspection, and sample testing of a five-media urine plate is exhibited. Each activity is performed per procedure -- these procedures are not exhibited. The label record is an actual label as printed on the urine plates -- the record sheet is passed through the printing machine. This technique reduces costs and eliminates human copying errors.

Batch Production Record (XLD)

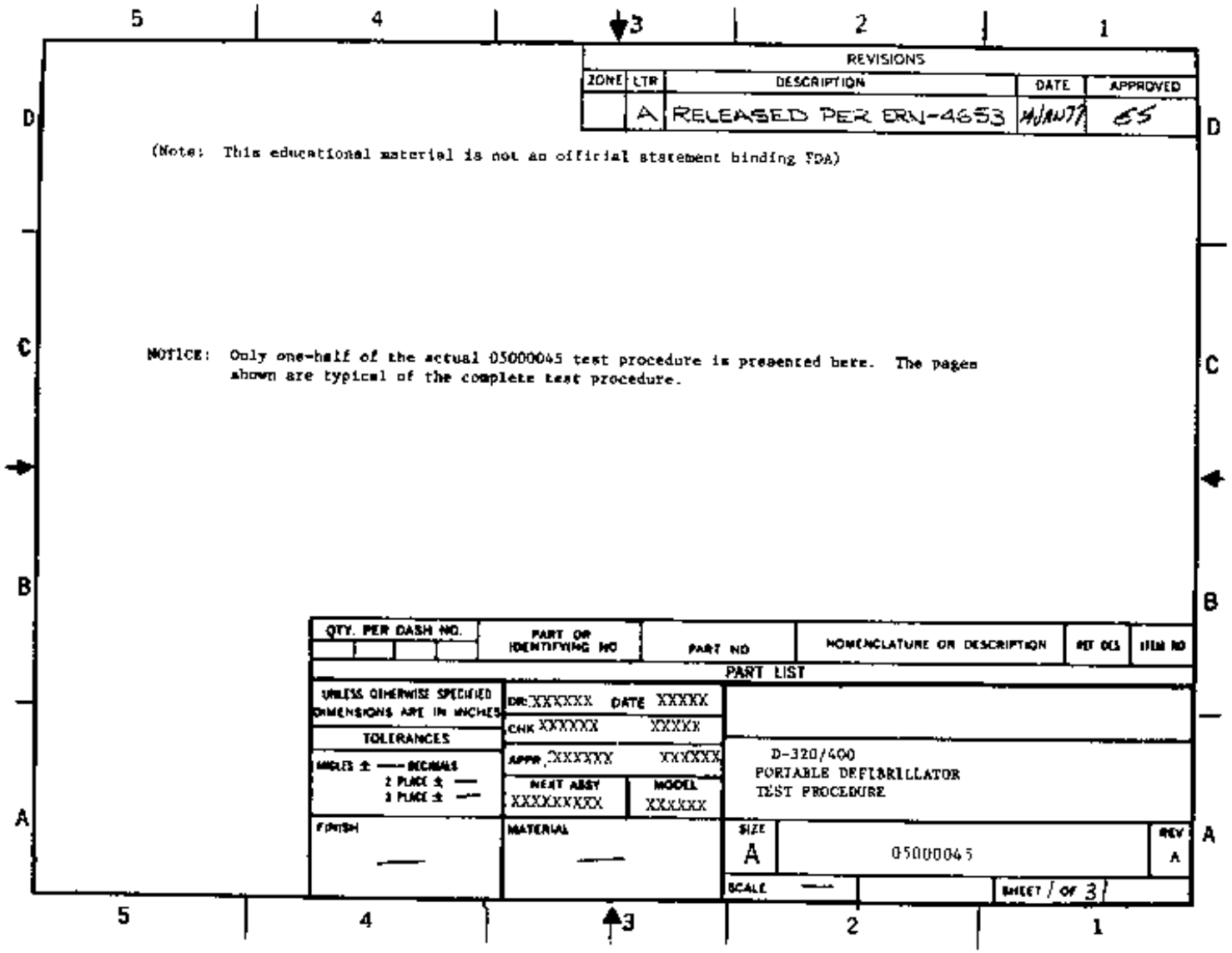
This exhibit is the batch production record of the XLD component used to fill one section of the five-part urine plate discussed above.

Batch Production Record (Thayer Martin)

This exhibit is a blank copy of the form used to record the batch production record for the Thayer Martin component used in the urine plate.

Batch Production Record (Blank form)

This exhibit is a form used to record the batch production record of various growth media. It could be used to record the production of XLD as mentioned above.



REVISIONS				
ZONE	LTR	DESCRIPTION	DATE	APPROVED
	A	RELEASED PER ERN-4653	4/JAN/77	ES

(Note: This educational material is not an official statement binding FDA)

NOTICE: Only one-half of the actual 05000045 test procedure is presented here. The pages shown are typical of the complete test procedure.

QTY. PER DASH NO.	PART OR IDENTIFYING NO	PART NO	NOMENCLATURE OR DESCRIPTION	MT OCS	ITEM NO
			PART LIST		

UNLESS OTHERWISE SPECIFIED DIMENSIONS ARE IN INCHES	DR XXXXXX DATE XXXXX		
TOLERANCES	CHK XXXXXX XXXXX		
ANGLES ± — DECIMALS 2 PLACE ± — 3 PLACE ± —	APPR XXXXXX XXXXXX	D-320/400 PORTABLE DEFIBRILLATOR TEST PROCEDURE	
	NEXT ASSY XXXXXXXXX	MODEL XXXXXX	
FINISH —	MATERIAL —	SIZE A	05000045 REV A
		SCALE —	SHEET 1 OF 3

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1.0 OBJECT:

To test the D-320, D-320W, D-400 or D-400W Portable Defibrillators for conformance to Engineering Specifications and to define the equipment and methods to perform these tests.

2.0 METHOD:

The Portable Defibrillator will be subjected to the following test sequence:

1. PC Boards Test
    1. Preliminary Test/Display Adjustments
    2. Burn-In
    3. Final Checks
2. Writer Tests
    1. Preliminary Tests
    2. Burn-In
    3. Final Tests
3. Final Tests
4. Battery Operation
5. Safety Tests

3. EQUIPMENT:

1. Scope, Tektronix Type 5103 or equivalent (DUAL TRACE SCOPE).
2. DVM, Fluke Type 8000A or equivalent.
3. Test Set #2033 (Bd. Test Set).
4. Heart Simulator, HS-1 or equivalent.
5. Function Generator, Krohn-Hite Type 5300 or equivalent.
6. Frequency Counter, HP Type 5512A or equivalent.
7. Noise Meter, HP Type 403 or equivalent.
8. Power Monitor, Sencore Type PM-157 or equivalent.
9. Variac, Power Stat Type 116 or equivalent.
10. Defibrillator Meter, Dempsey Type 429 or equivalent.
11. Pretested Adult Anterior Paddles (P/N 2499008201).
12. Electronic Stop Watch.
13. Pretested Scope Board, Defibrillator Board, Heart Rate Board, ECG Board and, if required, Writer Board.
14. Test Set #2030 (Stat Scope Test Set).
15. Test Plug #2036 (Int. Pad./Remote Chg.).
16. Adapter #2037 (Paddle Conn.).
17. Test Set #2041 (Writer Test Set).
18. Stylus Pressure Gauge.

4. DRAWINGS:

1.	Prod./Test Spec., Portable Defibrillator	A04300538
2.	Schematic, Portable Defibrillator	A04300211
3.	Schematic, Scope Board	C04300602
4.	P.W. Assy., Scope Board	E20300602

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5.	Schematic, Defibrillator Board	D04300207
6.	P.W. Assy., Defibrillator Board	E20300207
7.	Schematic, Heart Rate Board	C04300617
8.	P.W. Assy., Heart Rate Board	E20300617
9.	Schematic, ECG Board	D04300209
10.	P.W. Assy., ECG Board	E20300209
11.	Schematic, Writer Board	C04300210
12.	P.W. Assy., Writer Board	C20300210
13.	Schematic, Test Load Board	B04300618
14.	Assy., Test Load Board	C20300618
15.	QA Policy and Procedure, Section No. 26 (Elevated temperature burn-in of products).	
16.	Assy., Battery Pack.	
17.	Test Procedure, Systems Safety	A05000009

5.0 PROCEDURE:

NOTES: (1) WHEN TESTING THE D-320/400, HIGH VOLTAGES AND HIGH ENERGY LEVELS ARE PRESENT ON THE P.C. BOARDS AND CHASSIS MOUNTED COMPONENTS, ALL NECESSARY SAFETY PRECAUTIONS SHOULD BE TAKEN.

(2) The Printed Circuit Boards will be tested as a complete assembly, burned-in, re-tested, assembled into the main chassis (by production) and final tested as a complete portable defibrillator.

(3) Use an insulated blade screwdriver for making all the portable defibrillator adjustments.

(4) See APPENDIX 1 for the physical location of the pots and test points on the portable defibrillator.

(5) The Writer will be tested as a separate assembly, burned-in, re-tested and assembled into the D-320W/400W.

5.1 P.C. BOARDS TESTS

5.1.1 PRELIMINARY TESTS/POWER CONSUMPTION

5.1.1.1 Connect the P.C. Board assemblies into Test Set #2033, insuring the P.C. Boards slide into the P.C. guides. Connect the CRT connector on the Scope Board to the CRT and connect the two ribbon cables (P2 and P3) on the Test Set and P4 to the appropriate jacks on the DEFIBRILLATOR board. Connect the red clip lead to TP-12 on the defibrillator board.

5.1.1.2 CONNECT A JUMPER BETWEEN E3 AND E4 ON THE DEFIBRILLATOR BOARD AND CONNECT E4 TO GREEN WIRE GROUND.

5.1.1.3 Depress 1 pushbutton and release the remaining pushbuttons on the P.C. Boards. Rotate the high alarm control CW and the low alarm control CCW.

5.1.1.4 Connect the Scope to TP-10 on the SCOPE Board. Set the MAIN POWER switch on the test set ON. Depress the POWER ON pushbutton on the Test Set. The Scope should display a 15-20Vpp, 18-22 KHZ square wave within 1/2 second of turn-on, with rise and fall times < 3.5us. Two traces should be visible on the CRT within 15 seconds from the time power was applied to the unit.

5.1.1.5 Connect the DVM (DCV) between TP-19 (GND 1) and TP-9 (+10V) on the SCOPE Board. The DVM should read 9.8 ± 0.1V. Disconnect the DVM from the SCOPE Board.

5.1.1.6 Adjust the INTENSITY pot (R64) on the SCOPE Board to just below the point where the traces begin to unblank.

5.1.1.7 Adjust the "Y" ROT. pot (R89) on the SCOPE Board for a horizontal trace parallel to the bottom of the CRT.

5.1.1.8 Connect the HR simulator to the ECG board patient connector (simulator power off). Rapidly depress the MV pushbutton on the D-320/400. Adjust the SIZE control for ≈ 4 cm deflection.

5.1.1.9 When the MV pulses fill the screen horizontally, depress the FREEZE pushbutton on the HEART RATE Board. The MV pulses should "Freeze".

5.1.1.10 Adjust the FOCUS pot (R73) and the ASTIG pot (R60) on the SCOPE Board for the sharpest trace at the center of the display.

5.1.1.11 Adjust the "X" ROT. pot (R122) on the Scope Board until the MV pulses are parallel to the sides of the CRT.

5.1.1.12 Adjust the VERTICAL POSITION pot (R86) on the SCOPE Board so that the HR bar is ≈ 1/2 cm from the bottom of the CRT.

5.1.1.13 Adjust the HORIZONTAL POSITION pot (R92) on the SCOPE Board so that the HR pointer is at the left edge of the CRT.

5.1.1.14 Adjust the SWEEP RATE pot (R78) on the SCOPE Board so the right edge of the traces are at the right edge of the CRT.

5.1.1.15 Release the FREEZE button. The MV pulses should unfreeze.

5.1.1.16 Depress the RECORD pushbutton on the HR Board. The RECORD lamp on the Test Set should be on. Release the RECORD button. The RECORD lamp should be off.

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5.1.1.17 Adjust the Heart Rate Simulator for ≈ 120 BPM. The D-320/400 should display the ECG complex. Rotate the HIGH limit control on the Heart Rate Board fully CCW. Within three seconds after the heart rate pointer goes above the high alarm limit on the HR bar, the following alarm conditions should exist: (1) Steady audio tone, (2) The ALARM light on the HEART RATE Board should be flashing at ≈ 2HZ rate and (3) RECORD lamp on the Test Set on. Rotate the HIGH alarm limit fully CW. The alarm conditions should cease.

5.1.1.18 Rotate the LOW limit fully CW. Within three seconds after the limit passes the HR pointer, the previous alarm conditions should exist. Rotate the LOW limit fully CCW. The alarm conditions should cease.

5.1.1.19 With the DVM on DC volts, measure the voltage at the POWER IN side of F2 on the DEFIBRILLATOR Board. Note the value.

5.1.1.20 Set the MAIN POWER on the Test Set OFF. Remove F2 from the fuse holder and connect the DVM (2000 mADC Range) across the fuse holder.

5.1.1.21 Set the MAIN POWER on the Test Set ON. The DVM should read within the voltage/current limits specified in the following table at the voltage measured in step 5.1.1.19:

	12V	13V	14V	15V	16V	17V	18V	19V	20V
I MIN (mA)	332	298	277	259	243	228	216	204	194
I MAX (mA)	366	338	314	293	275	259	244	231	220

5.1.1.22 Set the MAIN POWER on the Test Set OFF. Disconnect the DVM from the fuse holder and insert the 0.5A fuse.

5.1.1.23 Set the Test Set main power switch ON. Momentarily depress the MAN. CHG. pushbutton on the Test Set. The DRY-LED on the test set should come on and the HR bar should be blinking. Rotate the CHG. pot on the Test Set slowly CW. The defibrillator bar should appear at the top of the CRT flashing alternately with the HR bar and increasing in length as the CHG. pot is rotated. Adjust the defib bar for full screen width. When the MAN button is depressed, a momentary audio tone should be present indicating the defib. is charging.

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D-320(W)/400(W)
DATA SHEET

D-320 ☐ -320W ☐
D-400 ☐ -400W ☐
120V,50/60HZ ☐ 240V,50/60HZ ☐
Remote Charge Option ☐

S/O_____
S/N_____
TESTED BY_____
DATE_____

HR BOARD S/N_____ REV_____
ECG BOARD S/N_____ REV_____
WRITER BD. S/N_____ REV___
SCOPE BD. S/N_____ REV___
DEFIB. BD. S/N_____ REV___

TEST NO.	TEST FUNCTION	DATA	COMMENTS	ACCEPT	REJECT
5.1.1	Preliminary Tests/ Power Consumption	V mA	See Table - Step 5.1.1.21		
5.1.2	P.C. Boards - Burn-In	Hrs	96 Hours Minimum @ 55°C		
5.1.3	P.C. Boards - Final Checks				
5.3.1	Resistance Checks	Ω	≤ 0.1Ω (Ground)		
5.3.2	Power Supply Check/ Preliminary Checks	V	9.8±0.1V		
5.3.3	ECG Transient Response		<5% of the 1MV pulse		
5.3.4	ECG Amp - Output Offset	mV	0±10mV		
5.3.5	ECG Amp Gain/ Display Gain/ Writer Gain	Vpp(ECG) Cmpp(DISP) Cmpp(WR) Vpp(ECG) Cmpp(DISP) Cmpp(WR)	1.0,+0,-0.2Vpp } MIN. 1.0,+0,-0.1cmpp } GAIN 1.0,+0,-0.1cmpp 1.0,+0.2,-0Vpp } MAX. 1.0,+0.1,-0cmpp } GAIN 1.0,+0.1,-0cmpp		
5.3.6	ECG Notch Filter Adjustments	mVpp	REF.		

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TEST NO.	TEST FUNCTION	DATA	COMMENTS	ACCEPT	REJECT
5.3.22	Defib. Remote Chg./ Int. Paddle Discharge				
5.4.1	Low Battery Adj./ Charge Time		Set at 12.30 VDC		
5.4.2	Charging Current/ Battery Drain	mA mA	150±30mA ≳ 300 (≲ 1000)mA		
5.4.3 *	Battery Life *	HRS	> 5 Hours with ECG Singal Only		
5.5.1.1	AC HI-Pot (Primary Power)		2500VAC for One Minute		
5.5.1.2	AC HI-Pot (Isolated Input)		2500VAC for One Minute		
5.5.1.3	Isolation (Paddles)		8KVDC from Paddles to Gnd.		
5.5.1.4	Risk Current	µA	≤ 10µA @ 120V/60HZ		
5.5.1.5	Green Wire Leakage	µA	≤ 50µA RMS @ 120V 50/60HZ		

* OPTIONAL

FINAL ACCEPTANCE _____

DATE _____

REVIEWED BY _____

DATE _____

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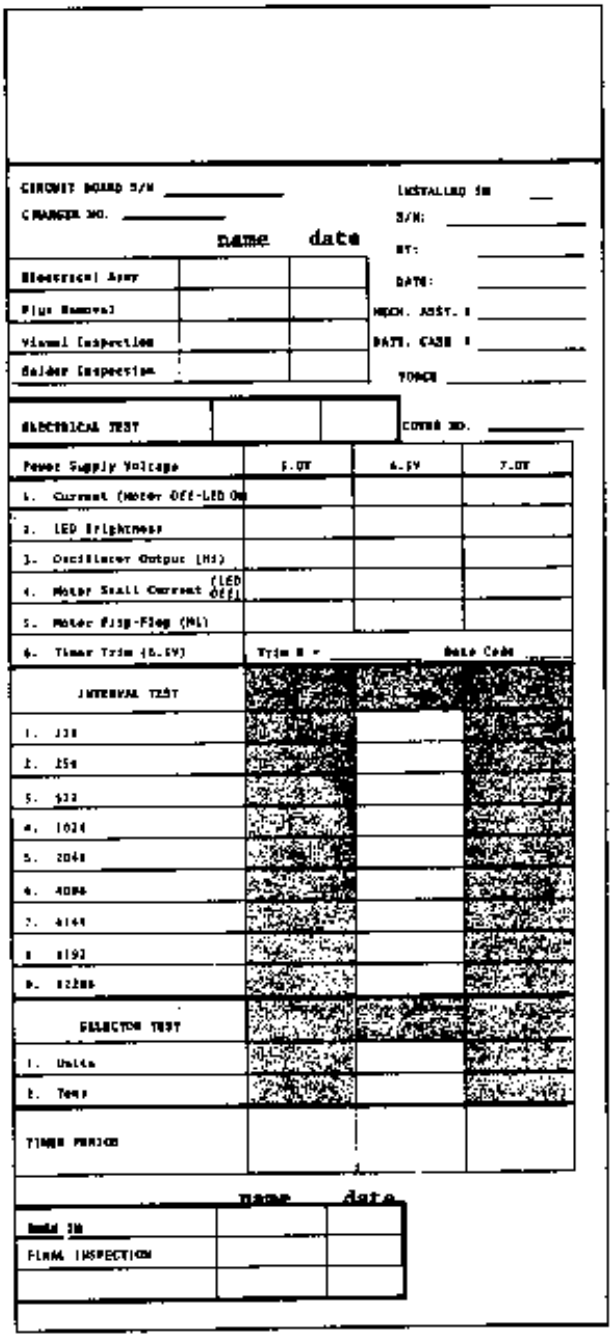
Sample: Electrical Inspection and Test DHR
Of A Printed Circuit Board Assemby



CIRCUIT BOARD S/N _____ INSTALLED IN ___

CHANGER NO. _____ S/N: _____

	name	date
Electrical Assy		
Pin Removal		
Visual Inspection		
Solder Inspection		

BY: _____

DATE: _____

MECH. ASST. # _____

DATE. CODE # _____

TORCH _____

ELECTRICAL TEST		

COVER NO. _____

Power Supply Voltage	5.0V	6.5V	7.0V
1. Current (Motor Off-LED On			
2. LED Brightness			
3. Oscillator Output (Hz)			
4. Motor Stall Current (LED Off)			
5. Motor Flip-Flop (Hz)			
6. Timer Trim (6.5V)	Trim # =		Date Code

INTERVAL TEST			
1. 128			
2. 256			
3. 512			
4. 1024			
5. 2048			
6. 4096			
7. 8192			
8. 16384			
SELECTOR TEST			
1. Units			
2. Tens			
TIMER PERIOD			

	name	date
Socket No		
FINAL INSPECTION		

This history record is used with a written test procedure (not shown). The test procedure includes the allowed range of values for each parameter.

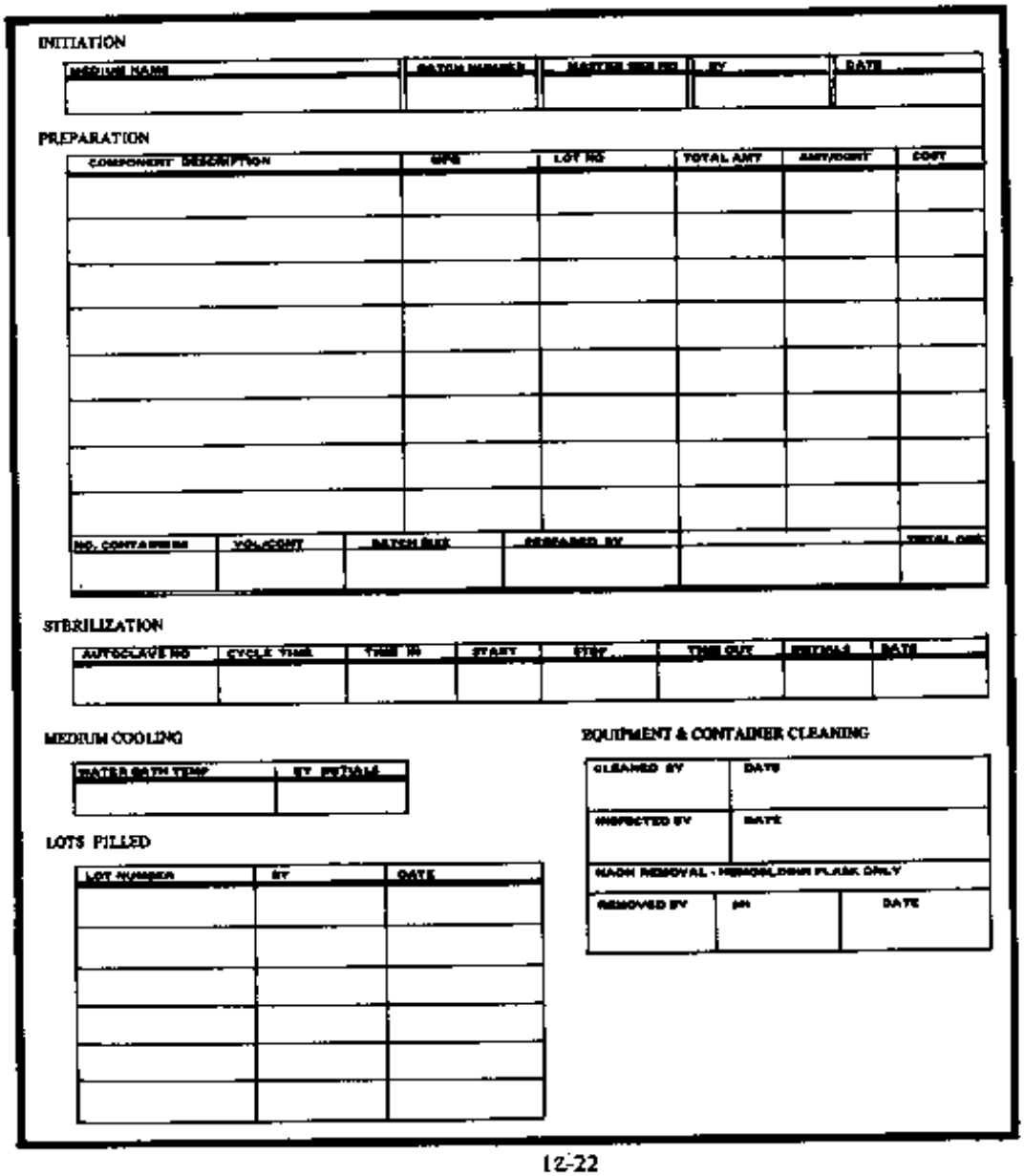
NOTE: Reverse side of card is used to record rework in comment form.

Rework Record	By

etc

12-18

BATCH PRODUCTION RECORD



INITIATION

MEDIUM NAME	BATCH NUMBER	MASTER BMR NO	BY	DATE

PREPARATION

COMPONENT DESCRIPTION	GMS	LOT NO	TOTAL AMT	AMT/CONT	COST

NO. CONTAINERS	VOL/CONT	BATCH SIZE	PREPARED BY		TOTAL GMS

STERILIZATION

AUTOCLAVE NO	CYCLE TIME	TIME IN	START	STOP	TIME OUT	INITIALS	DATE

MEDIUM COOLING

WATER BATH TEMP	ST. INITIALS

EQUIPMENT & CONTAINER CLEANING

CLEANED BY	DATE	
INSPECTED BY	DATE	
NaOH REMOVAL - ERLENMEYER FLASK ONLY		
REMOVED BY	pH	DATE

LOTS FILLED

LOT NUMBER	BY	DATE

12-22

13 PACKAGING

INTRODUCTION

The packaging industry is continuously evolving as medical product companies institute changes in the design, development, and manufacture of packaging systems. Thus, this chapter is not aimed at providing an all-inclusive list of packaging procedures and/or materials. Rather the goal is to instill an awareness of important packaging issues involving both design and manufacture. This chapter will also provide a basic understanding of the importance of validating processes and equipment, and the continuing need to maintain control of established packaging processes. The result should be a package that protects the device during handling and shipping, and from the environment and microorganisms until the package is opened. This includes allowing for any necessary sterilization. Packaging contains the product identification and other information as described in Chapter 11, Labeling. Packaging may also contain integral labeling and instructions for use or these instructions may be in a manual or package insert. Finally, when the consumer is ready to use this product, the package should be easy to open without compromising the quality of the device. In the end, a well designed package facilitates use of the device and contributes substantially to the overall appeal of the product. It makes sense for the manufacturer to invest in the development of a safe, user friendly package.

The design of the device, the labeling, the packaging and the manufacturing processes form the design output [820.3(g)]. These should be integrated. Manufacturers should consider the needs of the user as required by 820.30, Design Controls. Manufacturers should document these design outputs in the device master record then, procure, handle, store, and use the specified materials according to the device master record. FDA regulations are compatible with this total systems approach to device process design, production, packaging, and labeling.

Finally, manufacturers should perform quality assurance tests or acceptance tests on samples of the finished packages and, if sterilized, repeat the tests after sterilization. These tests should be based on a statistically valid sample to insure confidence that the packaging is capable of maintaining the integrity of the finished product. Where the device is very expensive, or only available in small quantities, the packaging tests may be performed on labeled, controlled packages that contain identified, rejected or simulated devices, as appropriate. The results of testing and/or inspection

should be recorded in the device history record. Correctly performing these activities can reduce or prevent customer complaints, recalls, and product liability actions.

PACKAGING DESIGN CONTROLS

Package design should be an integral part of the product development program. Waiting until the end of the development process to design packaging can result in severe delays in getting the product into distribution. The whole idea is to "build quality in." The total device and package system should be considered with respect to: device characteristics, sterilization process if any, sealing, labeling, secondary packaging, handling, shipping, environment, storage, federal regulations, and end use.

Defective packaging and seals have been a major cause of medical device recalls. This type of recall can often be avoided by correct package design including validation of the packaging and sealing processes. Packaging and sealing machines should be set up according to written procedures that are based on the known capability of the manufacturing system. It is important to be aware of the state-of-the-art in sealing methods and packaging materials, including their physical, chemical, biological, and compatibility characteristics and, of course, cost. "Wet" devices require high-barrier package materials and sealants with impermeability; resistance to solvents, grease, chemicals, and heat; and the ability to contain wetting agents, reagents, oils, or fragrances. Thus, the ability to seal in the presence of liquid components, if spillage occurs in the seal area, is important. Some peelable adhesives are highly solvent-resistant and also remain intact during radiation sterilization. If necessary, obtain guidance from suppliers, technical literature, and consultants. After the process has been developed and validated, the packaging aspect of production should be performed according to GMP requirements in order to maintain a state of control.

The design controls established by 21 CFR 820.30 and, particularly 820.3(g), define packaging as part of the device design output. This means the design phase of packaging shall include the application of quality systems requirements and the documentation of these applications. Control over package design shall be performed according to 820.30 for any Class II or Class III devices, devices automated with computer software, and the following Class I devices:

Device	Section
Catheter, Tracheobronchial Suction	868.6810
Glove, surgeon's	878.4460
Restraint, Protective	880.6760
System, Applicator, Radionuclide, Manual	892.5650
Source, Radionuclide Teletherapy	892.5740

Manufacturers of other Class I devices should establish and maintain procedures for ensuring that their device design is correctly translated into production specifications. They may use 820.30(h) as guidance. For these Class I devices that require design controls, packaging design is performed according to 820.130. The nature of the device as well as the sterilization method(s), intended use, shelf life, transport, and storage all affect package design.

The following activities are important to maintain control of package design:

1. **Planning for the design and development of packaging; and defining responsibility for implementation of design activities and controls. These plans should identify the different groups and activities providing input into the design process. Periodic review and approval is necessary as the package design evolves.**

2. **Establishing design input and output procedures, including review, documentation, signature, and date, that are appropriate for the intended use and the needs of the user and the patient. The procedures shall include safeguards for addressing concerns about the proposed designs.**

3. **Ensuring that design review procedures for all appropriate stages of the design development are conducted by qualified individual(s) and include an individual not directly responsible (NDR) for the design stage under review. This NDR person could be one of several people on the design review committee. The design identification, review results, reviewers, and date shall be documented in the design history file [820.30(j)].**

4. **Documenting design verification/validation to confirm that the design output meets the design input requirements in the design history file. This documentation must include the reviewers and date of review.**

5. **Establishing and maintaining design transfer procedures that insure that the package design is correctly translated into production specifications. The correct translation, of course, may be directly done as part of the design output.**

6. **After the package design is accepted, controlling changes according to company change control procedures. The manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation. A significant part of this control is achieved when design controls are followed.**

7. **Establishing a design history file to demonstrate the design was developed and approved according to plan. This, of course, should show that the design output meets the design input -- a fact which should be obvious from data presented during the final design reviews.**

Design controls require that a packaging design undergo considerable validation, review, and documentation. However, the end result is a smooth transfer into production with increased package safety and efficacy, resulting in greater customer satisfaction and cost savings and reduced liability.

In addition to the GMP requirements, manufacturers should always study current packaging practices for products similar to theirs to determine current favorable practices and to prevent user packaging problems. For example, customary use may dictate the use of double primary packaging for some sterile devices. Finally, any packaging used for medical devices should satisfy the end user or customer requirements, which automatically satisfies one of the design GMP requirements. This is a key point to be considered during the design phase.

User Preference

In the Medical Device and Diagnostic Industry magazine, the article, "Hospital-User Preference in Sterile Device Packaging," reports the results of a survey of nurses from operating room and

central services areas of hospitals. Several conclusions from the test results are listed below that should be of interest to sterile device manufacturers.

- **96 percent of the nurses had become "increasingly aware of the importance of quality packaging to infection control."**
- **90 percent said that packaging quality could influence their selection of a sterile medical device.**
- **87 percent wanted at least one package side to be transparent.**
- **95 percent preferred the adhesive to transfer from the lid to the lip of a tray when opened to indicate a broken seal.**
- **89 percent wanted sterilization process indicators printed on packages for sterile devices.**
- **99 percent said fiber-free opening of a sterile device package is important or very important.**
- **55 percent believed larger, high-profile devices would be best packaged in a tray with a peelable lid.**
- **55 percent preferred black printing on the package for easy reading.**

Package features that might favorably influence practitioners in the selection of a sterile medical device include:

- **clean, fiber-free opening,**
- **double packaging,**
- **printed process indicator,**
- **easy-open notches on chevron peel pouches, and**
- **lids with adhesive transfer.**

The nurses believe that being able to see and clearly identify a device is a "very important criterion of user preference." Also, as stated above, double primary packaging is preferred for some sterile devices.

PACKAGING MATERIALS

Fulfilling the design control procedures discussed above should include using the most appropriate packaging materials available for the device. Although requirements for components, device master records, environmental control, etc., that affect the selection and use of packaging appear throughout the Quality System (QS) regulation, the specific requirements for packaging are in section 820.130. Also the design requirements for Class II, Class III, and the few Class I devices that require design control extend to the broad requirements in 820.30. Device packaging and shipping containers should be designed and constructed to protect the device from adulteration or damage during the customary conditions of processing, storage, handling, and distribution. Closely related label integrity requirements are in section 820.120. Also, the quality of packaging should be considered in relation to the 21 CFR Part 812, Investigational Device Exemptions (IDE's) for clinical evaluations; Part 814, Premarket Approval (PMA) applications; Part 807, Premarket Notification

[510(k)] submissions and, of course, customer requirements. Failure to meet these packaging requirements renders a device adulterated and has resulted in recalls of sterile devices.

The package and device should be designed together so that all factors in the product and package system can be considered, such as device sharp edges and severe vacuum stresses. Some other factors to consider are:

End use	**Sterilization process**
Temperature	**Adhesives**
Moisture resistance	**Package porosity**
Thermal capacity	**Cling resistance**
Device composition	**Pressure**
Device size and shape	**Vacuum**

It is important that sterile devices and their packaging material meet the requirements of the sterilization process, package sealing method, and intended use. For example, radiation sterilization may discolor packaging and sealing materials, or reduce their functional capabilities. All plastics are somewhat affected by radiation sterilization, occasionally positively, frequently negatively. Consideration should be given to the effect produced and the radiation dose needed to produce an effect. Complete storage and stability data should be compiled for sterile device packaging subjected to radiation or should be obtained from the supplier.

Ethylene oxide (EO) sterilization requires packaging material of sufficient porosity to allow air to leave the package and the gas to rapidly permeate the package, sterilize the product, and then leave the package. Adverse levels of EO residues left on the device harm the patient. Air washing at the end of the cycle reduces residues. Evacuation of the sterilization chamber for air removal, gas fill, and air washing can induce package stress, particularly when the cycle calls for high temperature, pressure, and rapid pressure changes before and after the gas exposure (dwell) period.

PACKAGE VALIDATION

Package validation involves two separate validations: 1) the design validation of the package as a component of the device and 2) the process validation of the packaging process. Design validation uses evidence to establish what design specifications will conform with the user needs and the intended use(s) [830.3(z)(2)]. Process validation establishes by objective evidence that a process consistently produces a result or product that meets predetermined specifications [820.3(z)(1)].

The regulation, of course, refers to establishing evidence that the manufacturing steps involved in packaging the device will consistently produce packaging which meets specifications. For example, the process capability of packaging and sealing equipment should be determined during process validation and documented. Validation of the package design shall be performed under actual or simulated use conditions that show the package conforms to its stated intended uses. Risk analysis shall also be included where appropriate.

Design validation results shall include: the design identification, name of the individual(s) performing the validation, method(s) used, and the date. All of this information should be recorded in the design history file. If any significant change is made in the packaging or packaging operation after validation, the new process will need to be revalidated.

One of the most difficult aspects of package validation is determining how many samples to test. The goal is not to over test because of cost considerations while still running sufficient tests to provide statistically valid sampling. Statistical methods of analysis are important in process validation. The following decision tree from *Medical Device and Diagnostic Industry*, "Streamlining Package-Seal Validation," October 1992, provides various methods of statistical analysis. The manufacturer is challenged with determining which statistical method is most applicable to their individual needs. See Chart 1 below for possible methods of analyzing data. The resulting validation plan should identify, measure, and evaluate the key processes and variables that will require assessment to complete a validation or revalidation of the packaging and the packaging process.

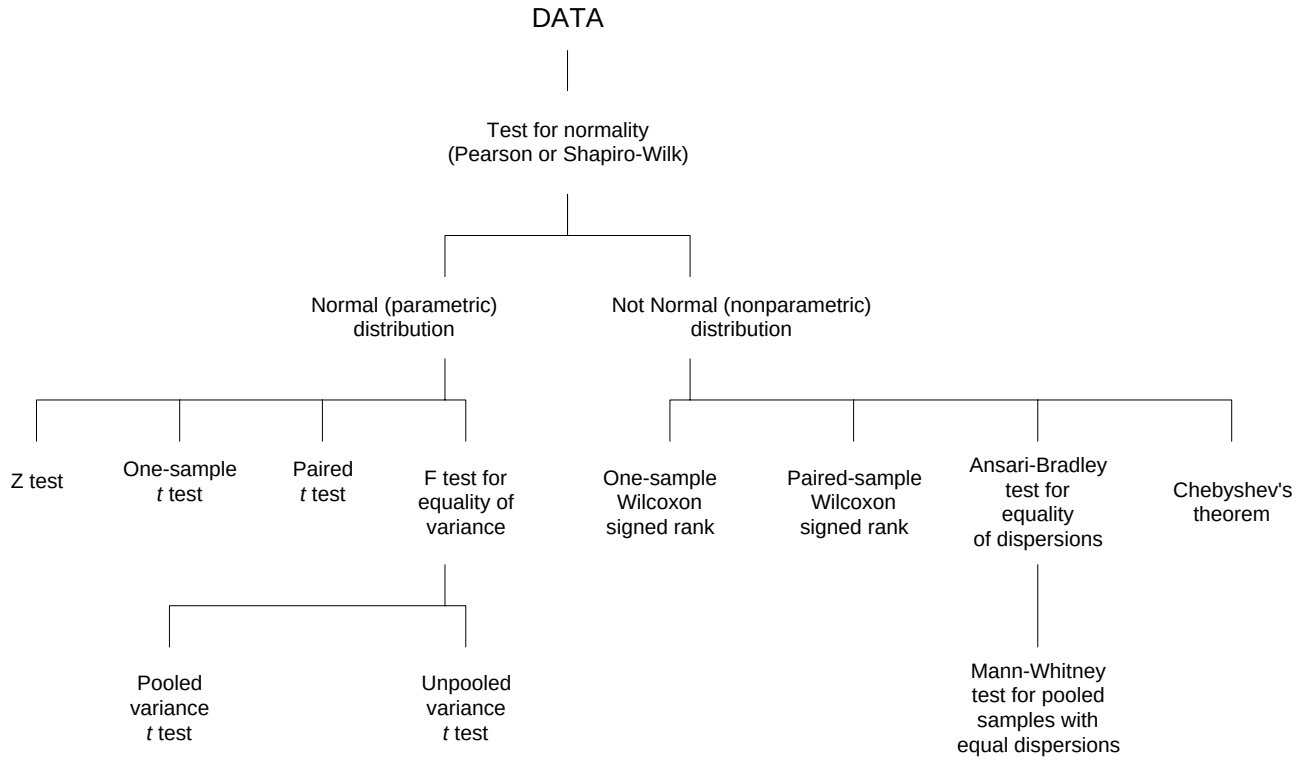


Chart 1 above shows various possible methods for analyzing data. Source: *Medical Device and Diagnostic Industry* periodical, October 1992.

PROCUREMENT, ACCEPTANCE, AND STORAGE

The packaging associated labeling, sealing methods, acceptance tests, etc., are part of the design output. These design output documents are part of the device master record. The device master record (820.181) should contain appropriate specifications so that the desired packaging components may be purchased, properly stored, and properly used. Suppliers are selected according to 820.50, Purchasing Controls. Manufacturers shall have adequate procedures for approval or rejection of all incoming packaging components such as adhesives, wrapping materials, corner protectors, pouches, cartons, etc. (820.80, discussed in Chapter 10). The supplier may test these components and provide the manufacturer with a protocol for testing and the test results for each batch (i.e., certificate of conformance to purchase specifications). The manufacturer could accept this specific data as

sufficient certification based on his assessment of the supplier along with the review of the certificate or order his own testing.

Incoming components should be examined for damage and identity before being used. At a minimum, this examination should include visual inspection. Thereafter, the packaging should be handled and stored in such a way that it is kept clean and safe from damage. Packaging and devices to be sterilized should, obviously, be kept clean before sterilization. For transfusion and infusion assemblies, devices that come in contact with circulating blood or cerebrospinal fluid, intraocular lenses and the surgical instruments used in their implantation, and any device labeled as "pyrogen free" or "nonpyrogenic," the manufacturer should carefully and appropriately control the environment to which the associated packaging materials are exposed in order to minimize bioburden and cellular debris from dead bacteria. Pyrogens primarily arise from cellular debris of gram-negative bacteria.

PACKAGING PROCESS

The packaging operation is a manufacturing process as described in Section 820.70, Production and Process Controls. Other GMP sections also apply to packaging including, but not limited to:

- **Receiving, In-Process and Finished Device Acceptance, section 820.80; and**
- **Distribution, section 820.160.**

These sections require adequate controls for components, processing, and test/inspection. The controls necessary for all devices should assure that:

- **labeling, whether a separate label or printed on the package, properly reflects the package contents and other labeling requirements;**

- **the packaging materials meet the device master record specifications;**

- **only devices approved for release are packaged and released; and**

- **the packaging operations are performed according to established procedures.**

The controls required will vary with the type of device packaged. For example, when a sterile device is packaged, a manufacturer's considerations should include:

- **environmental and personnel hygiene control;**
- **validated operating procedures for sealing equipment;**
- **inspection to assure package integrity and sanitation; and,**
- **stringent control of packaged devices marked "sterile" but not yet sterilized.**

For a product to be sterilized in-house, either a physical quarantine area or label control should be used to prevent shipment of devices marked sterile, but not yet sterilized. The required level of control is very high. The stringent control also extends to give-away samples not intended for actual use on patients -- samples should be sterile if so labeled because they might be used. One approach is to sell samples at zero cost so that the samples are subjected to all of the company finished product controls.

A written procedure is required by 801.150(e) for interstate contract sterilization. The purpose of this requirement is to help prevent the erroneous release of packaged and labeled "sterile" devices that are not yet sterilized even though they appear to be sterile and ready for release. Regardless of whether 801.150(e) applies, the QS regulation requires sufficient controls as necessary to prevent mixups in complex situations such as contract sterilization. For consistency, a contract is commonly used by manufacturers for interstate and intrastate shipments. Such a contract, and compliance with it, satisfies the applicable GMP requirements.

Section 820.181(d) requires that the device master record include packaging methods and processes. Written instructions should be provided to assure that the necessary controls are understood and consistently implemented. The need for, and the extent of, written instructions should be determined based on the complexity of the operation and the nature of the product. Some products such as radioimmunoassay test kits can deteriorate during packaging if the process is not timed properly. In such cases, written instructions should describe how the device(s) should be handled and expedited during packaging in order to prevent delays, and thus deterioration.

The procedure for testing and/or inspection of finished packages shall be written [(820.80(d)]. To the extent feasible, the testing of finished packages should be quantitative. The packaging of sterile devices should be tested and/or inspected before and after sterilization. This testing is done on a sampling basis. Sampling plans are valid only when a process is in a state-of-control; therefore, the device must be manufactured and packaged using a quality system as described in this manual.

EXHIBITS

The examples that follow will aid a company in preparing product packaging specifications and/or in purchasing standard packaging.

Product Specification: Pouch

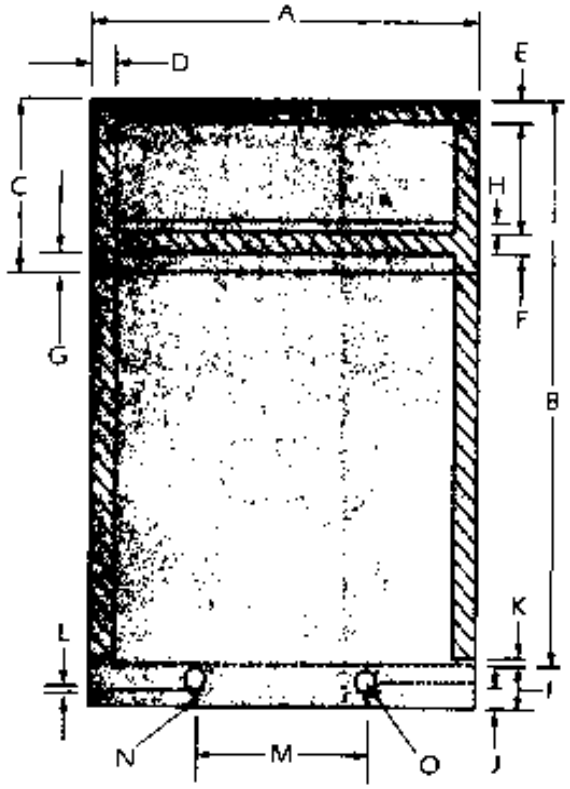
This form is used to purchase specific pouches from a standard family of pouches. The finished device manufacturer completes the form with the desired size, material, style, etc. The form refers to other documents which define the technical characteristics of the pouches.

Header Bag (Specification Form)

This specification for a header bag is set up as a checklist with the specifications on the right-hand side and a drawing of the bag on the left. The finished device manufacturer completes the form with the desired technical characteristics, assigns it a part number, and approves the finished document. An interesting idea reflected in this form is the important information block at the bottom of the form. This is a good way to remind personnel of pertinent information that is not strictly a part of the specification yet is vital to the control of this particular item.

HEADER BAG

Account:	Part Number:	
Item Description	Submitted by:	Date:
Approved by	Date	



CONSTRUCTION

Tyvek®/Paper/Other:
Film Gauge:
A. Bag Width
B. Sealed Length
C. Header Width
D..E.. F., Seal Width 3/8"
G. Header Lip 3/8"
H. Poly Lip 7/8"
I. Bag Lip
J. Wicket Position 3/4"
K. See seal length
L. Gap between slit and wicket hole 1/16" to 1/8"
M. Distance between wicket holes - see work order
N. Unslit distance between edge of bag and slit 1/16" to 3/16"
O. Wicket hole diameter - Standard 1/2" - must be clean cut
Printed: Yes No
PMS color(s):
Print Position:
Artwork Revision Date:
Additional Information:

TRACEABILITY: Medical Industries Inc. will maintain traceability (GMP) records of each lot back to the raw materials used, for the period of three years from date of manufacture.

IMPORTANT INFORMATION

Each packing slip and shipment will carry the following:

1. Customer Part Number
2. Quantity
3. Purchase Order Number (customer)
4. Product description
5. Order Status (complete or incomplete)
6. Vendor's Name
7. Cert. of Compliance

Each shipping container (carton) shall be labeled with the following information:

1. Carton number
2. Lot number (contains job and date)
3. Purchase order number
4. Size of unit (pouch)
5. Number of units contained (quantity)
6. Vendor's name
7. Product description
8. Product identification number

14 STORAGE, DISTRIBUTION, AND INSTALLATION

INTRODUCTION

The device Quality System (QS) regulation covers the manufacture, storage (820.150), distribution (820.160) and installation (820.170) of finished devices. For manufacturers and importers, distribution is one of the most important steps in their quality system. After a product is distributed, a manufacturer rarely has direct control over the product or how it is used. Thus, it is important that controls be in place to assure that only correctly labeled, packaged and approved finished devices are distributed and, if necessary, installed.

Holding and Distribution Procedures

Section 820.160 requires that the purchase order be reviewed to ensure that ambiguities and errors are resolved before devices are released for distribution. Manufacturers should have a program to reduce problems in this area. Marketing personnel should be adequately trained. Sales specification flyers and catalogs should be carefully written and kept current to reduce ordering problems. Incoming purchase orders should be checked and ambiguities and errors resolved. After receipt by appropriately trained personnel, orders should be reviewed immediately. If purchase orders are reviewed late in the manufacturing process or just before distribution, the value of the review may be significantly reduced. Where the customer includes specifications, each specified parameter should be checked against the corresponding parameter for the device. A checklist of device parameters may be a helpful tool for this review and should be filed with, or keyed to, the purchase order.

The QS regulation (820.60), Identification, requires manufacturers to set up and maintain identity control of their products from component receipt, production, distribution and through installation to prevent mixups. The regulation also requires that written procedures be provided for control and distribution of finished devices (820.160). The purpose of this requirement is to assure that only approved devices are distributed. Each manufacturer should determine what written procedures are needed to assure that only "approved for release" devices are distributed from the manufacturer. If a manufacturer believes written procedures will not contribute to assuring that only “approved for release” devices are distributed by their manufacturer, they should be able to

defend their decision. For example, the control is integrated into the activities required to package the device or to complete the device history record. This flexibility is allowed by section 820.5, Quality system, of the QS regulation.

Many manufacturers mark their released finished devices or identify them by location or packaging so that a simple visual check is sufficient to indicate whether the product is acceptable to release for distribution. For example, radiation-emitting electronic products are subject to a performance standard. The application of the certification label is often the last step in approving product release for distribution, and this label is used to distinguish such devices. After final release, the crating of large equipment is a very distinguishing feature. These types of operations may preclude the need for a separate written procedure.

For interstate contract sterilization, 21 C.F.R. section 801.150(e) requires a written agreement between the parties which details the necessary procedures to help prevent the erroneous release of packaged and labeled "sterile" but not yet sterilized devices that appear to be, but are not, ready for release. Regardless of whether 801.150(e) applies, the QS regulation requires controls, as necessary, to prevent mixups in complex situations such as contract sterilization. For consistency, a contract as described by 801.150(e) is commonly used by manufacturers for interstate and intrastate shipments. Compliance with such a contract satisfies the applicable GMP requirements. (See Chapter 10, Purchasing and Acceptance Activities, and Compliance Policy Guide 7382.830B for details.)

Sometimes manufacturers need to ship "finished devices" that have not been officially released because the final test data is not yet available. The critical factor is that the device still remains under the manufacturer's control. The most common example occurs when a manufacturer is waiting for the results from biological indicator tests. FDA permits manufacturers to ship such devices under quarantine to their own controlled warehouses where the devices may be readily recalled prior to any use, if the need arises. Manufacturers should not ship non-released devices to routine distributors or anyone outside of their direct control. Non-released products or products on "hold" for any quality reason should be controlled to prevent release. A suitable control is quarantine with a label on the units, pallets, etc., to indicate their status.

Warehouse Storage

Storage should always be done under systematic, orderly conditions (820.150). Manufacturers should use a first-in, first-out (FIFO) distribution system when fitness for use of a device deteriorates over time (820.150).

When a controlled environment is necessary to prevent abnormal deterioration, the environment should be specified, controlled, and monitored according to sections 820.70(c) (see Chapter 6, Buildings and Environment). Environmental specifications, such as storage temperature, should be included in the device master record.

The storage and handling of devices to be distributed may involve extensive activities (820.140 and 820.150). For example, damaged, recalled or returned devices should be suitably marked and segregated from devices acceptable for release (820.86). Returned devices should be handled and stored such that the cause of failure or other useful information is not destroyed. Returned defective devices should be formally investigated according to 820.100 Corrective and Preventive Action and any associated complaints investigated according to 820.198. Therefore, manufacturers will need

controls to assure that returned defective devices do not dead-end in the warehouse, but are expeditiously routed to the appropriate department for evaluation, investigation, conclusions and follow-up (see Chapter 15, Complaint Files).

Distribution Records

Quality System section 820.184, Device History Record (DHR), requires manufacturers of devices to maintain basic records for:

- **dates of manufacture,**
- **the quantity manufactured,**
- **quantity released for distribution,**
- **acceptance records,**
- **primary identification labels and labeling used, and**
- **any device identification and control number used.**

Section 820.160, Distribution, requires the following records:

- **name and address of the initial consignee,**
- **identification and quantity of devices shipped,**
- **date shipped, and**
- **any control number used.**

Some of the above information necessary for the distribution records is a duplicate of Device History Record (DHR) requirements. These duplications may be copied or transferred electronically from the DHR. If appropriate, a manufacturer may combine the records by adding the distribution information to the DHR.

In addition to the above requirements, manufacturers of implantable devices and life sustaining devices, the failure of which during use could result in significant injury to the user, are required to establish and maintain procedures for identifying with a control number each unit, lot, or batch of finished devices and, where appropriate, components (820.65). A partial list of traceable devices that meet this definition is printed at the end of this chapter.

Distribution records may be the same as, or part of, the normal business records. Generation of a separate record is not required unless the business records are not readily available, e.g., not maintained at the same establishment as the device history record and not readily retrievable electronically. Many manufacturers, also keep distribution records for billing and market survey purposes.

Manufacturers of radiological electronic products listed in 21 CFR 1002.1, Record and Reporting Requirements By Product, shall maintain distribution records that will enable them to trace specific products or production lots to distributors, or to dealers in those instances in which the manufacturer distributes directly to dealers (See 21 CFR 1002.30, Records to be Maintained by Manufacturers).

Distribution records shall be kept for a period of time equivalent to the design life and expected

life of the device, but in no case less than two years from the date of release for commercial distribution by the manufacturer [820.180(b)]. The intent of this requirement is support for potential repairs, corrective actions and recalls. Each manufacturer should make a prudent decision whether to discard records or keep all, or part, of them for a longer period. When requested, distribution records shall be made available to FDA investigators for review and copying during normal business hours.

DEVICE INSTALLATION

Section 820.170 on installation requires that each manufacturer establish and maintain adequate installation and inspection instructions and, where appropriate, testing procedures. The purpose of this requirement is to ensure that the device is properly installed and will perform as intended after installation. This regulation applies to medical device systems and complex devices that require set up and adjustment at the location where they are to be used. For example, before a diagnostic x-ray machine can be used, it has to be installed and adjusted and the performance checked. Cardiopulmonary bypass machines also require set up and adjustment at the user location. Manufacturers of such devices shall:

- **install the device, or have it installed by a representative;**
- **inspect and test, as appropriate, the device after installation to assure the device will perform as intended; or**
- **provide adequate instructions and procedures for proper installation by another party.**

These instructions and procedures for proper installation by the manufacturer's representative, user, or third party (820.170) shall include instructions on how to determine that the installed device is safe, performing satisfactorily and ready for use. Safety checks at installation refer to safety aspects directly related to the installation and setup activities and not to intrinsic safety features that have already been checked during final acceptance testing at the factory.

The instructions and procedures shall be distributed with the device or otherwise made available to the person installing the device. Such procedures and instructions are part of the device master record and generally include a checklist for the installer to make certain that all necessary installation and checkout activities have been performed correctly. The installer should complete the checklist. If available to the manufacturer, the filled-in checklist or other installation records are part of the device history record.

Installation and servicing are related activities. Therefore, see Chapter 16, Servicing, for more information.

EXHIBITS

Various forms to show that devices are finished and may be released or stopped from release and a list of some traceable devices are briefly described below and then exhibited.

Finished Product Release Form

This exhibit shows an example of a finished product release form which is actually a checklist for the manufacturing and QC departments of an in vitro diagnostic manufacturer to show that all required processes have been completed. The checklist acts as a reminder of the acceptance forms that are needed for a product and has space for the manufacturing and QC people to indicate that these forms have been completed and reviewed. Finally there is space for the designees to approve or disapprove the lot for release and for comments, if needed.

Release To Finished Goods/Shipping

This exhibit is a release form as described above except that it is for various hardware products. The employee writes in the specification for the product being released.

Product Shipping Hold

This exhibit is an example of a form used to stop the shipping of a finished device for reasons related to safety, performance, reliability, regulatory compliance, or other quality requirements.

Release From Product Shipping Hold

This is a form used to release a finished device from a stop shipment order. Because stop orders are always significant, this release form requires a signature by key management.

Partial List of Traceable Devices

This exhibit lists many of the devices for which a manufacturer must adopt a method of device tracking and the citation to 21 C.F.R. for the device.

It is required that implantable devices and life sustaining devices, whose failure during use as described on the label, could result in significant injury to the user, establish and maintain procedures for identifying with a control number each unit, lot, or batch of finished devices. Where appropriate, this traceability rule also applies to components. These procedures should facilitate corrective action. This identification should be documented in the device history record. Many of these devices were formerly called critical devices.

FINISHED PRODUCT RELEASE	Form No.	Rev.	Sheet 1 of 1
Form Approved by:		Date	
ECN notes:			

Title: AMYLASE SET			
Packaging lot number		Circle one CATALOG Number AM-389-01 AM-389-02	
The device history documents below were reviewed by → Circle one form number in 2, 5 & 7 below.		MFG ✓	QC ✓
1. Form # 9926	Product flow sheet		
2. Form # 1077 or 1078	Iodine solution		
3. Form # 1082	Substrate solution		
4. Form # 1083	Substrate tube filling sheet		
5. Form # 1084 or 1085	Iodine filling sheet		
6. Form # 1086	Packaging record		
7. Form # QC-PP-07 or QC-PP-01	Finished device specification		
Comments			
Sign. MFG Designee	APP. Yes or No		
Comments			
Signature QC Designee	Approved Yes or No		

RELEASE TO FINISHED GOODS/SHIPPING	Form # Release-110	Rev. B	Sheet 1 of 1
Form Approved by:		Date 4-15-1974	

ECN notes:

Type of Product: [ ] Cable [ ] Instrument [ ] Spare/Replacement part/assembly			
PRODUCT NAME	Part Number	Serial / Lot Number	
Inspection Specification Number		Revision	
PRODUCT STATUS		Circle yes or no ↓	
1. Final inspection complete per standards set forth in the QC manual and device inspection specification ?		YES	NO
2. Device history record packet present ?		YES	NO
If the answer to 1 or 2 is NO, return lot to Production.			
3. Has Final Inspection performed a simulated use test ?		YES	NO
4. An identified final test data sheet is with the unit ?		YES	NO
Comments			
Signature QC Designee Approved		YES	NO
Quantity Released		Date	

HOLD NUMBER:	DATE:

PRODUCT SHIPPING HOLD

BY QUALITY ASSURANCE DEPARTMENT

The product listed below is on SHIPPING HOLD and under NO circumstances is to be shipped from the factory or any field office without the written approval of the Director, Quality Assurance.

PRODUCT:

HOLD STARTING DATE:

CLASSIFICATION OF HOLD

[ ] EFFICACY **[ ] RELIABILITY** **[ ] STERILITY** **[ ] OTHER (describe)**	**[ ] SAFETY** **[ ] REGULATORY COMPLIANCE** **[ ] GOOF UP**

REASON FOR HOLD:

ACTION REQUIRED BEFORE RELEASE:

MDR/RECALL NOTES:

Sign., DIRECTOR, QUALITY ASSURANCE

DISTRIBUTION:

[ ] Manager, Shipping Department **[ ] National Field Manager** **[ ] General Manager** **[ ] Controller** **[ ] V.P. Corporate (if s/e problem)**	**[ ] Director, Manufacturing** **[ ] Division President** **[ ] Director, R & D** **[ ] Director, Marketing** **[ ] V.P. International (if int'l sales)**

HOLD NUMBER:	DATE:

RELEASE FROM PRODUCT SHIPPING HOLD

BY QUALITY ASSURANCE DEPARTMENT

The product listed below is RELEASED from SHIPPING HOLD.

PRODUCT:

HOLD RELEASE DATE:

REASON FOR RELEASE:

MDR/RECALL NOTES:

Sign., DIRECTOR, QUALITY ASSURANCE

DISTRIBUTION:

[ ] Manager, Shipping Department	**[ ] Director, Manufacturing**
[ ] National Field Manager	**[ ] Division President**
[ ] General Manager	**[ ] Director, R & D**
[ ] Controller	**[ ] Director, Marketing**
[ ] V.P. Corporate (if S/E)	**[ ] V.P. International (if Int'l sales)**

Partial List of Traceable Devices

CFR Cite	Classification Name of Device
	PART 868 -- ANESTHESIOLOGY DEVICES
868.1200	Indwelling blood oxygen partial pressure (P_{O2}) analyzer
868.2375	Breathing frequency monitor
868.5090	Emergency airway needle
868.5160(a)	Gas machine for anesthesia
868.5240	Anesthesia breathing circuit
868.5400	Electroanesthesia apparatus
868.5440	Portable oxygen generator
868.5470	Hyperbaric chamber (Monoplace)
868.5610	Membrane lung for long term pulmonary support
868.5650	Esophageal obturator
868.5720	Bronchial tube
868.5730	Tracheal tube
868.5740	Tracheal/bronchial differential ventilation tube
868.5750	Inflatable tracheal tube cuff
868.5800	Tracheostomy tube and tube off
868.5810	Airway connector
868.5830	Autotransfusion apparatus
868.5895	Continuous ventilator
868.5905	Noncontinuous ventilator (IPPB)
868.5915	Manual emergency ventilator
868.5925	Powered emergency ventilator
868.5935	External negative pressure ventilator
	PART 870 -- CARDIOVASCULAR DEVICES
870.1025	Arrhythmia detector and alarm
870.1330	Catheter guide wire
870.1360	Trace microsphere
870.1750	External programmable pacemaker pulse generator

CFR Cite	Classification Name of Device
870.1800	Withdrawal-infusion pump
870.3250	Vascular clip
870.3260	Vena cava clip
870.3300	Arterial embolization device
870.3375	Cardiovascular intravascular filter
870.3450	Vascular graft prosthesis of less than 6 millimeters diameter
870.3460	Vascular graft prosthesis of 6 millimeters and greater diameter
870.3470	Intracardiac patch or pledget made of polypropylene, polyethylene terephthalate, or polytetrafluoro-ethylene
870.3535	Intra-aortic balloon and control system
870.3545	Ventricular bypass (assist) device
870.3600	External pacemaker pulse generator
870.3610	Implantable pacemaker pulse generator
870.3620	Pacemaker lead adaptor
870.3650	Pacemaker polymeric mesh bag
870.3670	Pacemaker charger
870.3680	Cardiovascular permanent or temporary pacemaker electrode
870.3700	Pacemaker programmers
870.3710	Pacemaker repair or replacement material
870.3800	Annuloplasty ring
870.3850	Carotid sinus nerve stimulator
870.3925	Replacement heart valve
870.4320	Cardiopulmonary bypass pulsatile flow generator
870.4350	Cardiopulmonary bypass oxygenator
870.4360	Nonroller-type cardiopulmonary bypass blood pump
870.4370	Roller-type cardiopulmonary bypass blood pump
870.5200	External cardiac compressor
870.5225	External counter-pulsating device
870.5300	DC-defibrillator (including paddles)
870.5550	External transcutaneious cardiac pacemaker (noninvasive)
---	Percutaneous transluminal coronary angioplasty (PTCA) balloon

CFR Cite	Classification Name of Device
	dilation catheter
---	**Automatic implanted cardioverter defibrillator system**
	PART 872 -- DENTAL DEVICES
872.3640	**Endosseous implant**
	PART 874 -- EAR, NOSE, AND THROAT DEVICES
872.3620	**Ear, nose and throat synthetic polymer material**
874.3695	**Mandibular implant facial prosthesis**
874.3730	**Laryngeal prosthesis (Taub design)**
874.3820	**Emdolmphatic shunt**
874.3850	**Endolymphaic shunt tube with valve**
874.3930	**Tympanotomy tube with semipermeable membrane**
---	**Ear, nose, throat natural polymer-collagen material**
	PART 876 -- GASTROENTEROLOGY-UROLOGY DEVICES
876.3350	**Penile inflatable implant**
876.5270	**Implanted electrical urinary continence device**
876.5540	**A-V shunt cannula**
876.5630	**Peritoneal dialysis system and accessories**
876.5820	**Hemodialysis system and accessories, dialysate concentrate, hollow fiber capillary dialyzers, disposable dialyzers, high permeability dialyzers, parallel flow dialyzers, single coil dialyzers, twin coil dialyzers, single needle dialysis set, dialysate delivery systems**
876.5870	**Sorbent hemoperfusion system**
876.5880	**Isolated kidney perfusion and transport system and accessories**
876.5955	**Peritoneo-venous shunt**
46 FR 7566 (1/23/81)	**Urethral sphincter prosthesis**
46 FR 7566 (1/23/81)	**Urethral replacement**

CFR Cite	Classification Name of Device
PART 878 -- GENERAL AND PLASTIC SURGERY DEVICES	
42 FR 63474 (12/16/77)	Absorbable surgical sutures
42 FR 63474 (12/16/77)	Nonabsorbable surgical sutures
879.4520	Polytetrafluoroethylene (Teflon) injectable
878.3300	Surgical mesh
878.3500	Polytetrafluoroethylene with carbon fibers composite implant material
878.3530	Inflatable breast prosthesis
878.3540	Silicone gel-filled breast prosthesis
---	Implanted mammary prosthesis of composite saline and gel-filled design
878.3610	Esophageal prosthesis
878.3720	Tracheal prosthesis
878.4300	Implantable clip
878.4750	Implantable staple
---	Maxillofacial prosthesis
PART 880 -- GENERAL HOSPITAL AND PERSONAL USE DEVICES	
880.5130	Infant radiant warmer
880.5400	Neonatal incubator
880.5410	Neonatal transport incubator
880.5725	Infusion pump
---	Implanted infusion pump
PART 882 -- NEUROLOGICAL DEVICES	
882.5030	Methyl methacrylate for aneurysmorrhaphy
882.5150	Intravascular occluding catheter

CFR Cite	Classification Name of Device
882.5200	Aneurysm clip
882.5225	Implanted malleable clip
882.5250	Burr hole cover
882.5300	Methyl methacrylate for cranioplasty
882.5320	Preformed alterable cranioplasty plate
882.5330	Preformed nonalterable cranioplasty plate
882.5360	Cranioplasty plate fastener
882.5550	Central nervous system fluid shunt and components
882.5820	Implanted cerebellar stimulator
882.5830	Implanted diaphragmatic/phrenic nerve stimulator
882.5840	Implanted intracerebral/subcortical stimulator for pain relief
882.5850	Implanted spinal cord stimulator for bladder evacuation
882.5860	Implanted neuromuscular stimulator
882.5870	Implanted peripheral nerve stimulator for pain relief
882.5880	Implanted spinal cord stimulator for pain relief
882.5880	Epidural spinal electrode
882.5900	Preformed craniosynostosis strip
882.5910	Dura substitute
882.5950	Artificial embolization device
---	Lyophilized human (cadaver) dura mater
---	Stabilized epidural spinal electrode
---	Implanted intracranial pressure monitor
---	Totally implanted spinal cord stimulator for pain relief
	PART 884 -- OBSTETRICAL AND GYNECOLOGICAL DEVICES
884.5360	Contraceptive intrauterine device (IUD) and introducer
884.5380	Contraceptive tubal occlusion device (TOD) and introducer
	PART 886 -- OPHTHALMIC DEVICES
886.3300	Absorbable implant (scleral buckling method)
886.3400	Keratoprosthesis

CFR Cite	Classification Name of Device
886.3600	Intraocular lens
886.3920	Eye valve implant
	PART 888 -- ORTHOPEDIC DEVICES
888.3000	Bone Cap
888.3010	Bone fixation cerclage
888.3020	Intramedullary fixation rod
888.3025	Passive tendon prosthesis
888.3027	Polymethyllmethaccrylate (PMMA) bone cement
888.3030	Single/multiple component metallic bone fixation appliance and accessories
888.3040	Smooth or threaded metallic bone fixation fastener
888.3050	Spinal interlaminal fixation orthosis
888.3060	Spinal intervertebral body fixation orthosis
888.3100	Ankle joint metal/composite semi-constrained cemented prosthesis
888.3110	Ankle joint metal/polymer semiconstrained cemented prosthesis
888.3120	Ankle joint metal/polymer non-constrained cemented prosthesis
888.3150	Elbow joint metal/metal or metal/polymer constrained cemented prosthesis
888.3160	Elbow joint metal/polymer semi-constrained cemented prosthesis
888.3170	Elbow joint radial (hemi-elbow) polymer prosthesis
888.3180	Elbow joint humeral (hemi-elbow) metallic uncemented prosthesis
888.3200	Finger joint metal/metal constrained uncemented prothesis
888.3210	Finger joint metal/metal constrained cemented prosthesis
888.3220	Finger joint metal/polymer constrained cemented prosthesis
888.3230	Finger joint polymer constrained prosthesis
888.3300	Hip joint metal constrained cemented or uncemented prosthesis
888.3310	Hip joint metal/polymer constrained cemented or uncemented prosthesis
888.3320	Hip joint metal/metal semi-constrained, with a cemented acetabular component, prosthesis

CFR Cite	Classification Name of Device
888.3330	Hip joint metal/metal semi-constrained, with an uncemented acetabular component, prosthesis
888.3340	Hip joint metal/composite semi-constrained cemented prosthesis
888.3350	Hip joint metal/polymer semi-constrained cemented prosthesis
888.3360	Hip joint femoral (hemi-hip) metallic cemented or uncemented prosthesis
888.3370	Hip joint (hemi-hip) acetabular metal cemented prosthesis
888.3380	Hip joint femoral (hemi-hip) trunnion-bearing metal/polyacetal cemented prosthesis
888.3390	Hip joint femoral (hemi-hip metal/polymer cemented or uncemented prosthesis
888.3400	Hip joint femoral (hemi-hip) metallic resurfacing prosthesis
888.3410	Hip joint metal/polymer semi-constrained resurfacing cemented prosthesis
888.3480	Knee joint femorotibial metallic constrained cemented prosthesis
888.3490	Knee joint femorotibial metal/composite non-constrained cemented prosthesis
888.3500	Knee joint femorotibial metal/composite semi-constrained cemented prosthesis
888.3510	Knee joint femorotibial metal/polymer constrained cemented prosthesis
888.3520	Knee joint femorotibial metal/polymer non-constrained cemented prosthesis
888.3530	Knee joint femorotibial metal/polymer semi-constrained cemented prosthesis
888.3540	Knee joint patellofemoral polymer/metal semi-constrained cemented prosthesis
888.3550	Knee joint patellofemorotibial polymer/metal/metal constrained cemented prosthesis
888.3560	Knee joint patellofemorotibial polymer/metal/polymer semi-constrained cemented prosthesis

CFR Cite	Classification Name of Device
888.3570	Knee joint femoral (hemi-knee) metallic uncemented prosthesis
888.3580	Knee joint patellar (hemi-knee) metallic resurfacing uncemented prosthesis
888.3590	Knee joint tibial (hemi-knee) metallic resurfacing uncemented prosthesis
888.3640	Shoulder joint metal/metal or metal/polymer constrained cemented prosthesis
888.3650	Shoulder joint metal/polymer non-constrained cemented prosthesis
888.3660	Shoulder joint metal/polymer semi-constrained cemented prosthesis
888.3680	Shoulder joint glenoid (hemi-shoulder) metallic cemented prosthesis
888.3690	Shoulder joint humeral (hemi-shoulder) metallic uncemented prosthesis
888.3720	Toe joint polymer constrained prosthesis
888.3730	Toe joint phalangeal (hemi-toe) polymer prosthesis
888.3750	Wrist joint carpal lunate polymer prosthesis
888.3760	Wrist joint carpal scaphoid polymer prosthesis
888.3770	Wrist joint carpal trapezium polymer prosthesis
888.3780	Wrist joint polymer constrained prosthesis
888.3790	Wrist joint metal constrained cemented prosthesis
888.3800	Wrist joint metal/polymer semi-constrained cemented prosthesis
888.3810	Wrist joint ulna (hemi-wrist) polymer prosthesis

15 COMPLAINT FILES

INTRODUCTION

Section 820.3(b) of the Quality Systems regulation defines a complaint as "any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution." All medical device manufacturers are subject to the complaint requirements in 21 CFR Part 820, Quality System regulation and to the reporting requirements in 21 CFR Part 803, Medical Device Reporting (MDR) regulation. A complaint is any indication of the failure of a device to meet customer or user expectations for quality or to meet performance specifications. A complaint may be lodged against any finished device that had been released for distribution. Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications is subject to the provisions of 21 CFR 820.198, Complaint Files.

The sources of oral and written complaints are numerous. A manufacturer can receive this information via telephone, facsimile, written correspondence, sales representatives, service representatives, scientific articles, and FDA or internal analyses. Information will also be submitted by health care professionals, lay users, consumers, user facilities and distributors on the MedWatch Forms FDA 3500 and FDA 3500A.

Manufacturers are required to review, evaluate, and, when appropriate, investigate complaints, establish and maintain written procedures describing the process used to perform these activities, and designate a responsible individual or entity to perform these tasks. Complaints concerning death, serious injury or malfunctions, as defined in the MDR regulation, shall be reported to FDA as discussed later. Manufacturers of any class of medical devices are never exempted from the Quality System regulation complaint requirements (820.198) nor the general record requirements (820.180) which permit FDA review and copying of these records. Complaint file requirements are necessary to make certain manufacturers have adequate quality systems for investigating complaints and taking corrective action. Access to complaint files, device-related death and injury reports, and complaints about device defects enables FDA to determine if a manufacturer's quality system and corrective actions are adequate.

Manufacturers can identify problems with device component, labeling and packaging quality by several methods. To meet all GMP requirements these identification methods should include a review and evaluation of all complaints, failed devices, and service or repair requests. Complaints and service or repair requests are important sources of feedback information for a quality system. Finished devices that are returned for service or repair may meet the complaint requirements identified in section 820.198; therefore, these service or repair requests shall be evaluated to determine if they are complaints. Service or repair data shall be reviewed [820.200(b)&(e)] to identify systematic problems and problems that may qualify as complaints. When these problems are identified they should be processed as complaints according to the requirements in 820.198.

Complaint data, in conjunction with product audits, QA systems audits, operational analyses, inspection and test data, etc., is used by the quality assurance organization to:

- **identify poor performance in the overall quality system, particularly faulty design of devices, and faulty manufacturing processes;**
- **aid in implementing solutions to these quality problems;**
- **verify confidence in, and improve the performance of the quality system;**
- **improve the safety and performance of devices;**
- **reduce medical device reporting;**
- **reduce costs and improve production schedules;**
- **reduce employee confusion;**
- **improve customer relations by reducing the frequency of problems, complaints, and recalls; and,**
- **assure compliance with device regulations and consensus standards.**

Complaint Handling System

An effective complaint handling system is an extremely important part of any quality system. Even manufacturers who have not received complaints should be prepared to receive and process

them. Manufacturers should understand that any complaint received on a product shall be evaluated and, if necessary, thoroughly investigated and analyzed, and corrective actions shall be taken. The results of this evaluation should lead to a conclusion regarding whether the complaint was valid, what the cause of the complaint was, and what action is necessary to prevent further occurrences. Complaints cannot be ignored. They are an excellent indicator of problems with the use, design, and/or manufacture of a product. A single complaint that is thoroughly investigated may lead a company to take remedial or corrective action. It may also take an ongoing analysis of numerous complaints before a trend is spotted that causes a company to initiate changes in their product, labeling, packaging or distribution.

Using written procedures for handling complaints increases confidence that all complaints will be handled properly. Written procedures should be provided to employees to facilitate communication, maintain consistency, and reduce quality problems. Written procedures for the receiving, reviewing and evaluating of complaints by a formally designated unit shall be established and maintained in accordance with 820.198, Complaint Files, and 820.40, Document Controls, respectively. The procedures should include the need for complaints to be evaluated in accordance with 820.100, Corrective and Preventive Action.

The complaint files shall be maintained in accordance with the general record keeping requirements of 820.180. All complaint files are to be retained for a period of time equivalent to the design and expected life of the device, but in no case less than 2 years from the date of release for commercial distribution by the manufacturer. The written procedure should specify: authority; responsibilities; and the process to follow in receiving, reviewing, and investigating complaints. However, for very small manufacturers where division of work is minimal, and authorities and responsibilities are obvious, the GMP requirements as detailed in 820.198 in conjunction with appropriate forms may be sufficient as a protocol for handling complaints.

Although FDA does not specify a standard complaint handling system, the GMP requirements do specify certain actions that shall be included in any system. Manufacturers shall:

- **document, review, evaluate, and file all complaints;**
- **formally designate a unit or individual to perform these activities;**
- **determine if an investigation is necessary;**
- **record the reason if no investigation is made;**
- **assign responsibility for deciding when not to investigate; and,**
- **determine if the complaint requires an MDR report.**

Complaint Responsibility

Manufacturers shall formally assign responsibility for maintaining complaint files and conducting complaint investigations to individuals or an organizational unit. Under 820.25(b) it is the manufacturer's responsibility to ensure that personnel are properly trained to adequately perform their duties. These employees shall have the proper education and training to process complaints. Any difficulty noted in employees performing required tasks for proper complaint handling may be an indication that additional training is needed. Training shall be documented.

The person(s) assigned to review complaints should have a thorough knowledge of the product line in order to make an informed, reasonable decision as to the severity and significance of a complaint and to decide whether an investigation is necessary. If it is decided that an investigation is

not necessary, a record shall be made of the rationale used to arrive at this decision. The record must identify the individual responsible for making this decision.

Executive management should ensure that adequate resources are provided, including trained personnel, to the designated complaint handling unit within the company. The activities of the unit should be assessed on a regular basis, and corrections made if necessary.

MDR Reportable Complaints

Section 820.198(c) specifically requires that any complaint involving the possible failure of a device, labeling, or packaging to meet its performance specifications shall be reviewed, evaluated, and investigated unless such investigation has already been performed for a similar complaint and another investigation is not necessary. Also, section 820.198(d) further specifies that any complaint that requires an MDR report shall be promptly reviewed, evaluated, and investigated by a designated individual(s), and shall be maintained in a separate portion of the complaint files or clearly identified. However, if maintained separately a manufacturer should duplicate these serious complaints in the regular complaint file to assure that any analysis performed by product is inclusive of all complaints. Analysis by appropriate statistical methodology where necessary is a means of identifying quality problems. A single event, of course, may also be an indicator of a quality problem.

Complaint Records

FDA does not specify a standard method for recording or retrieving complaint information. Each manufacturer should develop a method for maintaining records of complaints and investigations that: is functional and economical, meets company needs, and meets requirements of the Quality System regulation. A two sided form is suggested when using hard copy to record complaints. One side may be used to record complaint information such as:

- **sequential number of the complaint;**
- **origin of the complaint;**
- **customer information;**
- **product information;**
- **any corrective actions already taken;**
- **details of the complaint;**
- **and dates, signatures, assignments, etc.**

The other side may be used to record:

- **instructions;**
- **investigations;**
- **analyses;**
- **conclusions;**
- **corrective action with respect to the product and to the customer;**
- **and dates, signatures, etc.**

A typical form is exhibited at the end of this chapter. The completed form should be stored in the complaint file which may be a physical or electronic file.

Investigation Records

The designated unit or person(s) responsible for maintaining the complaint file(s) shall prepare a written record of any investigations. This record shall include [820.198(e)]:

(1) The name of the device;
(2) The date the complaint was received;
(3) Any device identification(s) and control number(s) used;
(4) The name, address, and phone number of the complainant;
(5) The nature and details of the complaint;
(6) The dates and results of the investigation;
(7) Any corrective action taken; and
(8) Any reply to the complainant.

Also, the investigation record of any complaint that is being reported to FDA in an MDR report shall include a determination of [820.198(e)]:

(1) Whether the device failed to meet specifications;
(2) Whether the device was being used for treatment or diagnosis; and
(3) The relationship, if any, of the device to the reported incident or adverse event.

Section 820.198(e) requires the record of investigation to include any reply to the complainant. Manufacturers should send a reply to each complainant as a courtesy, but more important to prevent further misuse, injury or other adverse situations from recurring. However, because of the nature of the complaint, there may be cases where a reply is not necessary. In such cases, the record should state that no reply was made and the reason for not replying. When the problem was caused by misuse, it is very important to advise the user to help prevent further misuse. Also, the manufacturer should determine if inadequate labeling may have lead to misuse.

File Accessibility and Location

The GMP requirement states in 820.180 that "All records required by this part shall be maintained at the manufacturing establishment or other location that is reasonably accessible to responsible officials of the manufacturer and to employees of the Food and Drug Administration designated to perform inspections." "All records" includes complaint files and records of investigations. For complaint processing, responsible officials are general managers, complaint processors, QA managers, R&D and process engineers, and others who receive, process, investigate, and correct problems associated with complaints. Complaint files shall be reasonably accessible to FDA for review and copying. FDA has clear authority under Section 704(e) of the Food, Drug, and Cosmetic Act to inspect and copy all records required under section 519 of this Act.

The GMP requirement states that complaint files must be handled by a formally designated complaint unit. If the unit or individual(s) designated as responsible for investigating complaints is located away from the actual manufacturing site, the investigated complaint(s) and the record(s) of investigation shall be reasonably accessible to the manufacturing site. If a manufacturer's formally designated complaint unit is located outside of the United States, records required by this section shall be reasonably accessible in the United States at a location in the United States where the manufacturer's records are regularly kept or at the location of the original distributor.

When devices are produced for a manufacturer by a contract manufacturer, the manufacturer

should forward to the contractor copies of complaints and investigations that pertain to operations performed by the contractor. The contractor should maintain a complaint file and process complaints as discussed herein for the primary manufacturer.

Relabelers, importers, and others who distribute under their own name should forward complaints to the actual manufacturers, including foreign manufacturers, who are usually in the best position to resolve complaints on their own products.

Non-medical Complaints

Certain manufacturers' products may be used both as a medical device and for non-medical uses, for example lasers and motors. The complaints received from non-medical users do not necessarily have to be included in complaint files. However, if the non-medical product fails to meet specifications, then that report should be in the manufacturer's complaint file. This action would help assure compliance with 820.100, which requires identifying, recommending, or providing solutions for quality problems and verifying implementation of such solutions. The person receiving such complaints shall be trained [820.25(b)] to identify complaints that also affect those units used as medical devices.

Complaint Analysis

To facilitate detection of failure or defect trends, complaint files should be arranged in a manner that permits correlating present and past complaints for a particular product or product line. Thus, files are usually organized according to product or product lines. Manufacturers who do not organize complaint files by product or product line may have to search several files to find similar complaints or indications to identify problem trends. Complaints may be maintained in a computer file so that complaint data on a specific device or type of complaint can be readily accessed and analyzed. As appropriate, complaint analysis or their summaries should be included in the management review and the quality system [820.20(c)].

DEVICE FAILURE ANALYSIS

Manufacturers should process and analyze failed devices per 820.100. Section 820.100(a)(1) states that returned product is subject to corrective action. Failure analysis must be conducted by appropriately trained and experienced personnel [820.25(b)]. They should use a written procedure to assure that the process of device handling and analysis will not compromise the determination of the cause of the device failure. The failure investigation and analysis should determine the actual failure mechanism to the objective level necessary to correct the problem. When systematic failure has been diagnosed and corrective action established, a manufacturer need not analyze all additional devices that are returned with the same symptoms.

If a failure is determined to be related to safety and effectiveness, the deficiency should be determined, corrected and documented. If an investigation verifies a particular device deficiency and that this deficiency may exist in other products, the investigation should extend to determining its effect on other medical products.

Any corrective or preventive action taken shall be done following the requirements in 820.100.

FEEDBACK FOR QA SYSTEM

The more comprehensive a quality system is, the lower the probability of complaints occurring. However, in order for a quality assurance system to be dynamic or self correcting, data on quality problems from all sources should be fed back into the system. Complaints are a valuable source of data that can point to corrective actions.

Feedback data should flow into all operations that could be affected by the data and should be used to aid in device and process design evaluation and/or redesign, and to aid in improving the overall quality system program.

Regardless of the size of the formal quality system, the feedback data path in any company should be the same, that is, the data should flow into all affected operations even if some of these are not covered by the formal quality system or by FDA regulations.

COMPLAINT SOURCES

Complaints that shall be processed according to the GMP requirements may be received from:

- **customers by letter, credit memo, returned goods form, or phone;**
- **a manufacturer's representative, or other employees;**
- **the MedWatch voluntary reporting program;**
- **a service or repair request;**
- **journal articles; or**
- **the FDA.**

Complaints from any source shall be equally addressed by and be processed according to the company complaint policy and procedure. The company should make certain that market, sales, engineering, manufacturing, regulatory, installation, and service personnel are trained to properly identify and report complaints. These employees shall be made aware of this requirement according to section 820.25(b).

MEDICAL DEVICE REPORTING

In addition to the GMP requirements covering complaint handling and failure investigations, device
manufacturers shall also comply with the Medical Device Reporting (MDR) regulation, 21 CFR Part 803.

Who Must Report

The MDR regulation requires that all manufacturers of medical devices notify FDA when they become aware of a death or serious injury that may have been caused or contributed to by one of their marketed devices and/or any malfunction of one of their devices which, if it were to recur, would be likely to cause or contribute to a death or serious injury. These are the same complaints that the Quality System regulation requires a manufacturer to place in a separate portion of the complaint file or otherwise clearly identify [820.198(d)]. The MDR regulation is intended to supplement the Quality System regulation -- it is not meant to replace the GMP complaint and

failure investigation requirements.

When to Report

There are specific time limits within which the MDR reports shall be made. Any report of a device-related death, serious injury and malfunction shall be submitted within 30 calendar days from becoming aware of an MDR reportable event. To meet these requirements, manufacturers shall have an information handling system to assure that data are screened to determine what shall be reported to FDA. This system shall also be able to follow up this information quickly and accurately in order to comply with the MDR regulation. Manufacturers which have a good system for processing complaint and failure investigations such as described in this chapter will have the organization and data processing capabilities to meet the MDR requirements.

Manufacturers of medical devices are required to report a device related death, serious injury or malfunction to FDA using FDA Form 3500A, within 30 calendar days after becoming aware of the event. However, if the event necessitates remedial action to prevent an unreasonable risk of substantial harm to public health, then a report shall be submitted within 5 work days. Reports shall also be submitted when FDA notifies a manufacturer that 5-day reports involving a particular type of medical device or type of event are required.

The reporting process starts when an MDR reportable event is first recognized. Manufacturers are responsible for making sure their employees know how to recognize what may be reportable. Manufacturers should also emphasize that any employee may learn of an adverse event during a phone call, a sales visit, a professional conference, from correspondence received or from service/warranty orders.

Individual Adverse Event Reports

There are two types of individual adverse event reports that may be submitted by manufacturers. The 5 work day and 30 calendar day reports.

The 5-day report (803.53) is for MDR reportable event(s) that require a remedial action to prevent an unreasonable risk of substantial harm to the public health or where FDA has specified that a 5-day report is needed. This situation may be identified by the manufacturer or FDA:

- **If the manufacturer identifies the event and initiates a remedial action to prevent an unreasonable risk of substantial harm to the public health, a 5-day report is submitted instead of the 30-day report. Information not available within the five days should be provided in a supplemental report.**

- **If FDA identifies the event, the manufacturer will receive a written request directing them to file a 5-day report for all subsequent events of the same nature that involve similar devices for a specified time period. The FDA identification may be a result of its review of 30-day reports, inspection reports, user facility reports, etc.**

The 5-day period of reporting starts the day after any employee, who is a person with management or supervisory responsibilities over persons with regulatory, scientific, or technical responsibilities, or a person whose duties relate to the collection and reporting of adverse events, becomes aware that a reportable MDR event or events, from any information, including any

analysis, necessitate remedial action to prevent an unreasonable risk of substantial harm to the public health.

The MDR regulation defines remedial action as any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of a reportable event.

Not all remedial actions need to be submitted as 5-day reports. Only remedial actions that are necessary to prevent an unreasonable risk of substantial harm to the public health shall be submitted. If a remedial action is taken, but it is not done to prevent an unreasonable risk of substantial harm to the public health a 5-day report is not required. A 30-day report, however, may be required.

The discovery that a remedial action is necessary may be a direct result of one or more MDR reportable events occurring, or may be discovered through the performance of internal analyses using appropriate statistical or other acceptable methodologies for processing data.

Actions taken to fix a single device involved in the MDR reportable event are not remedial actions.

A 30-day report is required once a manufacturer receives or otherwise becomes aware of information that reasonably suggests that a device they have marketed:

(1) has or may have caused or contributed to a death or serious injury; or

(2) has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur.

The 30-day period for reporting starts the day after receipt by any employee of information that reasonably suggests that an MDR reportable event has occurred. FDA expects manufacturers to train their employees to recognize that they have received information on an adverse event and to know to whom in the company to forward this information for an MDR evaluation.

A manufacturer is NOT required to file an MDR report:

- **when it determines that a device related event did not occur, or**
- **when it determines that the device was made by another manufacturer.**

For the latter instance, the regulation requires the manufacturer to forward whatever information they have to FDA with a cover letter explaining that they did not manufacture the device so that FDA can send it on to the correct manufacturer. In this case, a 3500A should not be completed. Manufacturers may also voluntarily send a copy of this information to the manufacturer they identify as being the actual manufacturer.

Written MDR Procedures

In addition to having general complaint handling procedures, the MDR regulation (803.17) requires manufacturers to develop, maintain and implement written MDR procedures that at a minimum:

A. Set up internal systems for:

- timely and effective identification, communication, and evaluation of any events that may be MDR reportable;
- a standardized review process/procedure for determining when an event meets the criteria for reporting under the MDR regulation; and
- timely transmission of a complete MDR report to FDA.

B. Set up documentation and recordkeeping for:

- information that was evaluated to determine if an event was MDR reportable;
- all MDR reports and information submitted to FDA;
- any information that was evaluated when preparing the annual certification report; and
- systems that ensure access to information that facilitates timely follow up and inspection by FDA.

The MDR procedures should be either incorporated in the overall complaint handling procedure or be a companion to it. In either case these MDR procedures shall be clearly identified. If a companion procedure, it shall be incorporated by reference in the overall procedure. This will assure that all complaints are properly evaluated for MDR reporting.

Each manufacturer has certain discretion to determine the level of detail and depth of information that their written MDR procedures contain. FDA suggests that manufacturers provide policy and interpretation information regarding "typical" adverse events or product problems that may be MDR reportable. FDA also suggests that the procedures describe the investigation protocol that will be followed, e.g., two or three or four attempts will be made to contact the reporter either by phone, FAX or letter before an investigation is closed; that the complaint records will contain a concise but thorough description of the adverse event or product problem, that the complaint records will be legible, etc.

MDR Event Files

Each event that requires a determination regarding its MDR reportability shall be documented in an MDR event file (MEF) (803.18). This MEF will be one of the bases for establishing compliance with the requirements of the MDR regulation. Files are to be accessible to FDA personnel for review and evaluation, be as complete as possible, and are to clearly document MDR related actions and decisions. The following information should be in the MEF to assure that it complies with the MDR requirements:

a) The original or a copy of the initial record complaint/event. This record should include the available information needed to complete the Form FDA 3500A. The record may be documentation of a telephone call, a letter or facsimile, a service report, documents related to a lawsuit, a voluntary FDA 3500 received from a health care professional or consumer, or mandatory FDA 3500A received from a User Facility and/or a Distributor, etc.

b) Copies of any records documenting the manufacturer's attempts to follow-up and obtain missing or additional information about the event. When information cannot be obtained an explanation shall be made part of the file.

c) Copies of any test reports, laboratory reports, service records and reports, records of investigation, etc.

d) Copies of all documentation involving the final assessment of the event, any deliberations and/or decision making processes used to determine whether an MDR report was or was not needed. When applicable, the final assessment should indicate what action, if any, the manufacturer has taken to assure that the cause of the event is corrected or otherwise mitigated.

e) Copies of all FDA 3500A forms submitted to FDA, when applicable. This includes a copy of any FDA 3500A forms received from User Facilities and Distributors.

f) Documents verifying that the event has been evaluated in accordance with the applicable requirements of the QS regulation, sections 820.100 and 820.198.

g) References to any other relevant documents or information used during assessment.

How To Maintain MDR Event Files

The MEF can be written or electronic files. They may make reference to other information that was used during the investigational process, in lieu of copying and maintaining duplicates in the file. Any referenced material is to be made available to FDA personnel for review, copying and verification.

Each MEF shall be retained for a period of two (2) years from the date of the event or a period of time equivalent to the expected life of the device, whichever is greater. Each MEF file shall be maintained for this period of time even if the device is no longer sold/distributed by the manufacturer.

The MEF may be maintained as part of the complaint file required by 21 CFR Section 820.198, however, the MEF files shall be prominently identified.

ADDITIONAL MDR GUIDANCE

Manufacturers should refer to the guidance document entitled, "Medical Device Reporting for Manufacturers," for further information on how to comply with this requirement.

REPORTS OF REMOVALS AND CORRECTIONS

At the time of completion of this manual, FDA has not published a final rule implementing its authority under section 519(f) of the Act to require reports of removals and corrections. It is important to note, however, that the agency published a proposal to implement this authority at 59 FR 13828 (March 23, 1994). A final rule based on the proposed rule may require reporting different from or in addition to that required by the Quality System and MDR regulations.

EXHIBITS

Exhibits are described below which follow in the order described.

Complaint Processing Procedure and Forms

This sample procedure is used to establish and help implement a system for processing routine complaints for devices. The customer complaint form mentioned in the sample procedure is essentially the same as the form, "customer/device complaints," in the next exhibit. Nowadays the complaint log shown on sheet 3 of 5 is easily maintained on a computer.

An example of a complaint recording form follows the complaint processing procedure.

The form titled "Customer Complaint" can be used to record most complaints.

If it matches a manufacturer's needs, the complaint form may be used as is. Also, it may be modified to meet specific needs. If the form is modified or a new one is developed, a manufacturer should make sure the resulting form is consistent with the GMP requirements and consistent with any complaint handling policy and/or procedures being used at the manufacturer.

MedWatch Forms

A copy of the MedWatch 3500A is included at the end of this chapter. This form may be photocopied for submitting reports.

***** SAMPLE PROCEDURE *****

C O M P A N Y L O G O		**Sheet 1 of 5**
Title Complaint Processing Procedure	**SOP Number**	
Prepared by	**Date Prepared**	
Approved by	**Date**	**Rev**
ECN Notes		

PURPOSE: To establish and implement a procedure and forms for recording customer complaints, analysis, response, and corrective action.

POLICY: It is the policy of our company that all complaints regarding safety, performance, or quality of our products or services will be subject to management review and/or investigation and will result in prompt response and corrective action where indicated.

SCOPE / DEFINITION: This policy is applicable to and must be complied with by all personnel who receive a customer complaint, including personnel in Sales and other departments.

A "complaint" is any indication of the failure of a device to meet customer or user expectations for quality or to meet performance specifications. Thus, any written, oral, or returned goods expression of dissatisfaction relative to the identity, quality, durability, reliability, safety, effectiveness, or performance of any device manufactured by this manufacturer would be considered a complaint.

Types of complaints intended to be covered by this policy are as follows:

1. **PRODUCT PERFORMANCE: the product in some way does not perform to user's expectation or to any level of performance conveyed to the customer by printed labeling or verbally by company employees.**

2. **PRODUCT SAFETY: all safety complaints are covered by this procedure.**

3. **PRODUCT RELIABILITY: failure rate or need for service adjustments greater than user expectation, i.e. beyond the tolerable level of expected wear or malfunction.**

4. **PRODUCT APPEARANCE: visual defects inconsistent with the user's expectations for a medical device.**

5. **GENERAL COMPLAINTS: order or shipping error, delayed or unacceptable response to problems, unfulfilled promises, etc.**

6. **MDR REPORTABLE COMPLAINTS: all complaints involving device-related deaths, serious injuries and malfunctions. (See Policy/Procedure No. XXX for handling of MDR reports.)**

FORMS USED: Customer/Device Complaint and Analysis and Complaint Log

PROCEDURE: Upon receipt of a customer complaint, the recipient completes side one of a CUSTOMER/DEVICE COMPLAINT form and, if the complaint is written, attaches the complaint letter to the form. The recipient then gives the form, with any attachments, by the next day to the Manager of Quality Assurance.

IMPORTANT COMPANY POLICY: Where a complaint requires immediate corrective action or response to a customer, the complaint recipient must either take the required action or communicate with the proper person to take the required action. It is the responsibility of the recipient of any complaint to see that the customer receives a response -- nothing in the following procedure relieves him or her of this responsibility.

Quality Assurance:

1. **Assigns a sequential complaint number and enters the complaint into the Complaint Log.**

2. **Determines and notes on the complaint form the person to whom the complaint is to be assigned for investigation and/or corrective action and the date a response is required from the assignee.**

3. **Notes any specific instructions to the assignee.**

4. **Distributes a copy to appropriate Department(s) as checked on side 1 of the complaint form.**

5. **Makes 2 copies of all sides of the in-process form and attachments, and distributes:**

   Original to the Assignee.
   One copy to the "UNDER INVESTIGATION" complaint folder.

The Assignee:

1. **Performs the investigation and/or corrective actions and records the results on the form; and attaches any investigation records. If no investigation was done the reason why must be recorded and the name of the approving official documented.**

2. **Returns the original of the in-process form to QA.**

Quality Assurance:

1. **Records on the Analysis side:**

   If no action is taken, the reason for inaction should be recorded on the analysis form.

   Any additional corrective action taken or directed by QA.

   Whether an MDR report was submitted to the FDA.

   The nature and date of any response made to the originator or the customer. If this response is written, a copy of the letter or FAX is attached to the analysis form.

   The final disposition of the complaint.

   QA signature and date.

2. **Records the final disposition of the complaint on the complaint log.**

3. **Files the completed form in the appropriate complaint file for the type of device involved; and discards the copy previously filed in the "UNDER INVESTIGATION" complaint folder.**

4. **Distributes the complaint log monthly to Staff and specifically involved departments. This log should include a trend analysis of complaints for the month correlated with trends noted in previous months.**

***** SAMPLE RECORD *****

COMPLAINT LOG			Sheet 3 of 5	MONTH , 19
Seq. No.	**Date Rec'd.**	**Type Device**	**COMPLAINT**	**DISPOSITION**

*** SAMPLE RECORD*** Sheet 4 of 5 of Procedure No. _____

CUSTOMER COMPLAINT (Side 1) SEQUENTIAL NO._____

Device Name _____ Model Number _____

Catalog Number_____ Lot Number _____

Distributor_____

Name of Complainant_____ Phone No. _____

Complainant Address_____

Complaint Received by_____

Title_____ Date Received_____

By: ☐ Visit ☐ Phone ☐ Letter ☐ Sales ☐ Credit Memo ☐ Other_____

COMPLAINT ABOUT

☐ Sterility_____

☐ Particulate Matter Type_____ Location_____

☐ Defect_____

☐ Packaging_____

☐ Labeling_____

☐ Patient Death_____

☐ Patient Injury_____

☐ Product Malfunction_____

☐ Other (specify)_____

Comments/Description of Event_____

_____

ATTACHMENTS ☐ Implicated Sample ☐ Associated Sample ☐ Letter
Received By QA Mgr_____ Date _____

Assigned To_____ Response Due_____

Instructions_____

_____

_____

Distribution: ☐ Quality Control ☐ Engineering ☐ Production ☐ QA ☐ Sales ☐ Service

*** SAMPLE RECORD*** Sheet 5 of 5 of Procedure No. _____

CUSTOMER ANALYSIS (Side 2) SEQUENTIAL NO._____

Device Name _____ Model Number _____

Catalog Number_____ Lot Number _____ Date of Complaint Report_____

Name of Complainant_____

Nature of Complaint_____

ASSIGNEE EVALUATION
Date(s) Evaluation Performed_____

Evaluation Results_____

_____

_____

_____

☐ Copy of evaluation attached

CONCLUSIONS
☐ Device Defective ☐ Device Failed to Meet Specifications ☐ Improper Use
☐ Shipping Damage ☐ Repair Request

☐ Other(specify)_____

_____

ACTION/REPLY TO COMPLAINANT
☐ None. Reason for no action_____

_____

☐ Recalled. FDA phoned on - Date_____ Spoke to_____

☐ Complaint Committee Informed on - Date _____ ☐ MDR Filed on - Date _____

☐ Referred to_____for Further Investigation or Correction

☐ Replaced ☐ Repaired ☐ Credited ☐ Letter Sent ☐ Sales Follow Up

☐ Reason for No Reply_____
NOTES:

FINAL DISPOSITION_____

Reviewed by: Quality Assurance_____Date___

If requested: Engineering_____Date___

Production_____Date_____

Form Approved: OMB No. 0910-0291 Expires: 12/31/94
See OMB statement on reverse

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Page ____ of ____

Mfr report #

UF/Dist report #

FDA Use Only

A. Patient information

1. **Patient identifier** In confidence

2. **Age at time of event:** or **Date of birth:**

3. **Sex** ☐ female ☐ male

4. **Weight** _____ lbs or _____ kgs

B. Adverse event or product problem

1. ☐ **Adverse event** and/or ☐ **Product problem** (e.g., defects/malfunctions)

2. **Outcomes attributed to adverse event** (check all that apply)
   - ☐ death _____ (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other: _____

3. **Date of event** (mo/day/yr)

4. **Date of this report** (mo/day/yr)

5. **Describe event or problem**

6. **Relevant tests/laboratory data**, including dates

7. **Other relevant history, including preexisting medical conditions** (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. **Name** (give labeled strength & mfr/labeler, if known)
   #1
   #2

2. **Dose, frequency & route used**
   #1
   #2

3. **Therapy dates** (if unknown, give duration) from/to (or best estimate)
   #1
   #2

4. **Diagnosis for use** (indication)
   #1
   #2

5. **Event abated after use stopped or dose reduced**
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply

6. **Lot #** (if known)
   #1
   #2

7. **Exp. date** (if known)
   #1
   #2

8. **Event reappeared after reintroduction**
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply

9. **NDC #** – for product problems only (if known)
   – –

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

D. Suspect medical device

1. **Brand name**

2. **Type of device**

3. **Manufacturer name & address**

4. **Operator of device**
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: _____

5. **Expiration date** (mo/day/yr)

6.
   model # _____
   catalog # _____
   serial # _____
   lot # _____
   other #

7. **If implanted, give date** (mo/day/yr)

8. **If explanted, give date** (mo/day/yr)

9. **Device available for evaluation?** (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on _____ (mo/day/yr)

10. **Concomitant medical products** and therapy dates (exclude treatment of event)

E. Initial reporter

1. **Name, address & phone #**

2. **Health professional?** ☐ yes ☐ no

3. **Occupation**

4. **Initial reporter also sent report to FDA** ☐ yes ☐ no ☐ unk

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

FDA Form 3500A (6/93)

Medication and Device Experience Report

(continued)

Refer to guidelines for specific instructions

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

Page ____ of ____

FDA Use Only

F. For use by user facility/distributor–devices only

1. **Check one**
☐ user facility ☐ distributor

2. **UF/Dist report number**

3. **User facility or distributor name/address**

4. **Contact person**

5. **Phone Number**

6. **Date user facility or distributor became aware of event** (mo/day/yr)

7. **Type of report**
☐ initial
☐ follow-up # ____

8. **Date of this report** (mo/day/yr)

9. **Approximate age of device**

10. **Event problem codes** (refer to coding manual)
patient code ____ – ____ – ____
device code ____ – ____ – ____

11. **Report sent to FDA?**
☐ yes ____ (mo/day/yr)
☐ no

12. **Location where event occurred**
☐ hospital
☐ home
☐ nursing home
☐ outpatient treatment facility
☐ outpatient diagnostic facility
☐ ambulatory surgical facility
☐ other: ____ specify

13. **Report sent to manufacturer?**
☐ yes ____ (mo/day/yr)
☐ no

14. **Manufacturer name/address**

G. All manufacturers

1. **Contact office – name/address** (& mfring site for devices)

2. **Phone number**

3. **Report source** (check all that apply)
☐ foreign
☐ study
☐ literature
☐ consumer
☐ health professional
☐ user facility
☐ company representative
☐ distributor
☐ other: ____

4. **Date received by manufacturer** (mo/day/yr)

5. (A)NDA # ____
IND # ____
PLA # ____
pre-1938 ☐ yes
OTC product ☐ yes

6. **If IND, protocol #**

7. **Type of report** (check all that apply)
☐ 5-day ☐ 15-day
☐ 10-day ☐ periodic
☐ Initial ☐ follow-up # ____

8. **Adverse event term(s)**

9. **Mfr. report number**

H. Device manufacturers only

1. **Type of reportable event**
☐ death
☐ serious injury
☐ malfunction (see guidelines)
☐ other: ____

2. **If follow-up, what type?**
☐ correction
☐ additional information
☐ response to FDA request
☐ device evaluation

3. **Device evaluated by mfr?**
☐ not returned to mfr.
☐ yes ☐ evaluation summary attached
☐ no (attach page to explain why not) or provide code: ____

4. **Device manufacture date** (mo/yr)

5. **Labeled for single use?**
☐ yes ☐ no

6. **Evaluation codes** (refer to coding manual)
method ____ – ____ – ____ – ____
results ____ – ____ – ____ – ____
conclusions ____ – ____ – ____ – ____

7. **If remedial action initiated, check type**
☐ recall
☐ repair
☐ replace
☐ relabeling
☐ other: ____
☐ notification
☐ inspection
☐ patient monitoring
☐ modification/ adjustment

8. **Usage of device**
☐ initial use of device
☐ reuse
☐ unknown

9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:

10. ☐ **Additional manufacturer narrative** and/or 11. ☐ **Corrected data**

16 SERVICING

INTRODUCTION

The requirements in the Quality System (QS) regulation govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use. Servicing covers the maintenance and repair of finished, distributed devices.

The intent of the quality system regulation is to assure that servicing is correctly performed and verified according to company specified requirements such that the serviced device is suitable for the intended use and that service information is collected and analyzed to help correct any quality system problems and device design, manufacturing, labeling, or packaging problems.

The basic servicing requirements are in 820.200, Servicing. However, there are related requirements throughout the QS regulation. For example, service procedures are documented per 820.181, Device Master Record; and servicing activities and/or data may lead to complaint analysis per 820.198, Complaint Files, or require corrective and preventive action per 820.100.

When a finished device manufacturer contracts with another supplier to perform their servicing, such service (or service contractor) must meet the applicable purchasing and servicing requirements in the QS regulation.

Interfaces

There are interface requirements in the QS regulation that apply to service functions. Section 820.30(b), Design and Development Planning, requires that each manufacturer shall establish and maintain plans that describe or reference the design and development activities and define responsibility for implementation. The plans shall identify and describe the interfaces with different

groups or activities that provide, or result in, input to the design and development process.

The preamble clarifies the fact that these requirements extend to service functions by stating: the plan shall identify and describe the interfaces with different groups or activities that provide, or result in, input to the design process. Many organization functions, both inside and outside the design group, may contribute to the design process. For example, interfaces with marketing, purchasing, regulatory affairs, manufacturing, service groups, or information systems may be necessary during the design development phase. To function effectively, the design plan should establish the roles of these groups in the design process and describe the information that should be received and transmitted.

Therefore, for medical devices that require servicing, during appropriate activities such as design input and design reviews, service requirements and ease of service should be considered; and service managers, senior service technicians, etc., may need to participate in these design functions. Such participation may reduce the:

- **need for maintenance and repairs;**
- **time to perform repairs,**
- **need for special tools; and**
- **cost of repairs.**

Reducing the time for repairs and the need for special tools usually reduces production assembly time and manufacturing costs.

SERVICE PERSONNEL

Service shall be conducted by appropriately trained and experienced service personnel (820.25) in order to:

- **assure, to the extent feasible, that the process of device handling, diagnosis, and repair will not compromise the determination of the root cause of the device failure;**
- **identify and correct the failure;**
- **correctly report the service information; and**
- **identify and report data related to a serious incident or adverse event.**

The repair diagnosis should also try to determine, and/or provide adequate data to assist analysts in determining, the actual failure mechanism to the objective level necessary to correct or reduce the problem.

Thus, service personnel must be trained to adequately perform their assigned maintenance, repair, and reporting responsibilities. Such training shall be documented (820.25). The training is also performed in accordance with the instructions and procedures established under 820.200 for performing and verifying that servicing meets the specified requirements. Because servicing must be verified, service personnel must be made aware of defects and errors that may be encountered as part of their job functions (820.25). This training requirement usually does not require separate or additional training because basic training to perform repairs emphasizes the identification of defects and errors.

SERVICE REQUIREMENTS

The QS regulation does not require that a manufacturer service a device. The decision to service or have their devices serviced is left to the manufacturer. When a manufacturer specifies that they will perform service or contract to have service performed, such service must meet all of the applicable QS regulation requirements. Such a manufacturer shall establish and maintain instructions and procedures for performing and verifying that the servicing meets the manufacturers specified requirements. Section 820.200, Servicing, states:

(a) Where servicing is a specified requirement, each manufacturer shall establish and maintain instructions and procedures for performing and verifying that the servicing meets the specified requirements.

(b) Each manufacturer shall analyze service reports with appropriate statistical methodology in accordance with 820.100.

(c) Each manufacturer who receives a service report that represents an event which requires reporting to FDA under part 803 or 804 of this chapter shall automatically consider the report a complaint and shall process it in accordance with the requirements of 820.198.

(d) Service reports shall be documented and shall include:

(1) The name of the device serviced;
(2) Any device identification(s) and control number(s) used;
(3) The date of service;
(4) The individual(s) servicing the device;
(5) The service performed; and
(6) The test and inspection data.

INSTALLATION

Where service and installation are required by a manufacturer, both of these product activities are related and so are the QS requirements for both. Section 820.170 *Installation* states:

(a) Each manufacturer of a device requiring installation shall establish and maintain adequate installation and inspection instructions, and where appropriate test procedures. Instructions and procedures shall include directions for ensuring proper installation so that the device will perform as intended after installation. The manufacturer shall distribute the instructions and procedures with the device or otherwise make them available to the person(s) installing the device.

(b) The person installing the device shall ensure that the installation, inspection, and any required testing are performed in accordance with the manufacturer's instructions and procedures and shall document the inspection and any test results to demonstrate proper installation.

Some manufacturers use their service department or a service contractor to install their medical devices. Servicing may also include re-installing a device. As shown in Table 16.1, Comparison Of Servicing And Installation Requirements, the QS requirements for installation in 820.170 essentially parallel the requirements for service in section 820.200. For example, The QS regulation includes detail of the reporting requirements for servicing; for installation, the manufacturer chooses the information to document. However, from a practical viewpoint, each manufacturer would choose to have the same information documented. Thus, as appropriate, a manufacturer may combine most of

their service and installation QS activities.

CONTRACT SERVICE

When a finished device manufacturer contracts with another supplier to perform their servicing, such service (or service contractor) must be obtained per the applicable requirements in 820.50, Purchasing. Each manufacturer shall establish and maintain procedures to ensure that all purchased or otherwise received services conform to specified requirements. Each manufacturer shall establish and maintain the requirements, including quality requirements, that are to be met by contractors. Each manufacturer shall:

(1) Evaluate and select potential contractors on the basis of their ability to meet specified requirements, including quality requirements. The evaluation shall be documented.

(2) Define the type and extent of control to be exercised over the contractors based on the evaluation results.

(3) Establish and maintain records of acceptable contractors.

Each manufacturer shall establish and maintain data that clearly describe or reference the specified service requirements, including quality requirements. Purchasing data shall be approved in accordance with 820.40.

A major portion of the purchasing requirements are met when the manufacturer meets the servicing requirements in section 820.200(a) which states:

(a) Where servicing is a specified requirement, each manufacturer shall establish and maintain instructions and procedures for performing and verifying that the servicing meets the specified requirements....

That is, these specified requirements, service instructions and procedures, and device verification procedures may be used together with other information such as the finished device description to help show a prospective contractor the scope and expected quality of the servicing that is being contracted.

Table 16.1 COMPARISON OF SERVICING AND INSTALLATION REQUIREMENTS

SERVICING	INSTALLATION
(a) ... establish and maintain instructions and procedures for performing and verifying that the servicing meets the specified requirements.	**(a) ... establish and maintain adequate installation and inspection instructions, and where appropriate test procedures.**
(a) .... and verifying that the servicing meets the specified requirements.	**(a) Instructions and procedures shall include directions for ensuring proper installation so that the device will perform as intended after installation.** **(b) The person installing the device shall ensure that the installation, inspection, and any required testing are performed in accordance with the manufacturer's instructions and procedures and ...**
(b) Each manufacturer shall analyze service reports with appropriate statistical methodology in accordance with 820.100.	
(a) ... establish and maintain instructions and procedures for performing and verifying that the servicing meets the specified requirements.	**(a) ... The manufacturer shall distribute the instructions and procedures with the device or otherwise make them available to the person(s) installing the device.**
(d) Service reports shall be documented and shall include: **(1) The name of the device serviced;** **(2) Any device identification(s) and control number(s) used;** **(3) The date of service;** **(4) The individual(s) servicing the device;** **(5) The service performed; and** **(6) The test and inspection data.**	**(b) The person installing the device shall ensure that the installation, inspection, and any required testing are performed in accordance with the manufacturer's instructions and procedures and shall document the inspection and any test results to demonstrate proper installation.**
(c) Each manufacturer who receives a service report that represents an event which requires reporting to FDA under part 803 or 804 of this chapter shall automatically consider the report a complaint and shall process it in accordance with the requirements of 820.198.	

SERVICE EQUIPMENT

Section 820.20(b)(2) *Resources* requires each manufacturer to provide adequate resources, including the assignment of trained personnel, for management, performance of work, and assessment activities to meet the requirements of this part. As appropriate, adequate resources include service instructions, service procedures, supporting DMR drawings, and service equipment. Service equipment includes equipment to perform the repair and to verify the proper performance of the serviced devices. Service equipment may include complex apparatus; however, it also includes any simple jigs, test cables, special hand tools, etc., as needed to meet the service needs of specific medical devices.

Servicing and Installation both require verifying that the device meets acceptance criteria. Therefore, appropriate and calibrated test equipment should be used. Section 820.72, Inspection, Measuring, and Test Equipment, requires that each manufacturer to ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results. Each manufacturer shall establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained. The procedures shall include provisions for handling, preservation, and storage of equipment, so that its accuracy and fitness for use are maintained.

When establishing service and installation procedures, each manufacturer needs to comply with the Inspection, Measuring, and Test Equipment requirements, as appropriate, in order to assure that the serviced/installed device performs as intended. For example, a manufacturer may need to determine which service equipment, if any, needs to be calibrated in a laboratory and which, if any, may be calibrated using the self-contained internal calibrators. Also, the manufacturer may need to select equipment that is capable of producing valid results after being subjected to repetitive and demanding service.

SERVICE PROCEDURES

If any are required, maintenance needs, schedules, and procedures are developed as part of the device design program. Some preventive maintenance tasks and their schedules may result from reliability studies performed during design development.

Repair procedures are based in part on design verification and finished device test and inspection procedures, production procedures, and rework procedures. Other aspects of repair procedures are developed by qualified technical personnel and senior repair technicians. The development of procedures may involve inserting failures or defects and having another person find and repair them. The problems, discovery methods, and rework techniques are documented.

For redesigns, existing maintenance and/or repair procedures that are known to be current and correct may be referenced in the new service procedures or these may be renumbered and copied into the new procedures.

Identifying defective subassemblies or modules in the device and replacing them with good modules is a common servicing practice. The defective assembly is discarded, sent to be investigated, or is repaired at a designated facility with the necessary environmental conditions and facilities; test equipment and tools; component availability; trained rework employees; etc. This approach should

also be covered by appropriate procedures.

The development of service procedures includes the development of appropriate service reporting forms.

Service instructions and procedures must be documented per 820.40. They are part of the device master record (DMR). Typical DMR documents (820.181) that are needed for service or that may be modified for service include:

- **device specifications including appropriate drawings, component specifications, and software specifications;**

- **quality assurance procedures and specifications including acceptance criteria and the quality assurance equipment to be used; and**

- **installation, maintenance, and servicing procedures and methods.**

These DMR documents usually cover:

- **what the device does;**
- **theory of operation;**
- **operating instructions;**
- **safety;**
- **device specifications;**
- **component specifications, identification, and nomenclature;**
- **test apparatus, jigs, and special tools;**
- **typical failure modes and conditions;**
- **how to identify and isolate failures;**
- **test points where specific parameters may be measured;**
- **removal and replacement of parts;**
- **testing and inspecting (verifying) the repaired device;**
- **re-installation procedures, if applicable; and**
- **reporting forms.**

ACCEPTANCE STATUS

Each manufacturer shall identify by suitable means the acceptance status of devices to indicate whether it has been service and whether it conforms with the acceptance criteria. The conformance is determined by the procedures established inaccordance with 820.200(a).

The identification of acceptance status shall be maintained throughout servicing of the device to ensure that only devices which have passed the required acceptance activities are distributed, used, or installed (820.86). Identification is usually done by appropriate information on a decal, tag, or an attached pouch that contains the service request and/or report.

If a decal is left on the serviced device, for the next request and service, the decal can provide immediate information about the last service date, etc.

SERVICE REPORTS

Service activities shall be documented by service personnel and sent to the manufacturer according to the manufacturer's established procedures. As mentioned, service reports shall include:

(1) the name of the device serviced;
(2) any device identification(s) and control number(s) used;
(3) the date of service;
(4) the individual(s) servicing the device;
(5) the service performed; and
(6) the test and inspection data.

The device identification should be specific regarding the revision level, modification version, software version, etc., of the device in order to support analysis of the service data.

The test and inspection data should verify that the servicing meets the manufacturer's specified requirements. That is, the serviced device did, or did not, meet the acceptance criteria. (See Acceptance Criteria below.)

The service reports should also include information such as:

- **device owner, address and phone number;**
- **specific location of the device;**
- **any unusual environmental conditions;**
- **any evidence of damage or misuse;**
- **if the device failed to meet specifications;**
- **if the device was being used for treatment or diagnosis;**
- **relationship, if any, of device to a death or serious injury; and**
- **date of last service and service report number, if known.**

SERVICE REPORT ANALYSIS

Each manufacturer that performs servicing shall analyze service reports with appropriate statistical methodology in accordance with 820.100, Corrective and Preventive Action, which requires manufacturers to establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements for analyzing service records and other sources of quality data to identify existing and potential causes of nonconforming product or other quality problems. The primary intent is to identify the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems; and to verify or validate the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device.

Failure and service report analysis should be conducted by appropriately trained and experienced personnel (820.25). Such personnel are also one of the resource requirements in 820.20(b)(2).

The analysis of service reports or subsequent analysis of the same or equivalent device(s) should be designed to determine the actual failure mechanism or quality problem to the objective level necessary to correct the problem.

When systematic failure has been diagnosed and corrective action established, a manufacturer

need not analyze all additional devices that are serviced or returned with the same symptoms.

The analysis of service reports is totally dependent on the quality of the data in the reports. Therefore, it is very important that service training cover reporting so that the resulting reports are correct, complete, understandable, and easy to analyze.

The service reports for routine service requests for maintenance, adjustment, or repair of damage or failure resulting from long use, misuse or accident, usually do not need the same level of analysis as for other failures. However, some requests for service may appear to be routine when, in fact, they may be for unusual conditions that warrant attention. For example, service requests because of rapid wear, unusual problems, unusual maintenance, or development of hazardous conditions should receive a complete analysis in order to determine if corrective action is needed in the preventive maintenance procedures, design, labeling, manufacturing processes, etc. Enough information should be obtained from the customer to determine whether the request is for routine maintenance or the device is to be serviced for other reasons.

Parts Shipping Trends

As appropriate manufacturers should periodically (e.g., monthly) examine shipping records for repair parts. Any increases in shipment of specific parts due to unknown reasons should be analyzed to determine if a significant failure problem exists. Manufacturers have identified quality problems by this simple, low-cost technique.

COMPLAINTS

Service requests for repairing or investigating an event that allegedly resulted in a death or serious injury shall also be investigated as a complaint. Section 820.200(c) requires that each manufacturer who receives a service report that represents an event which requires reporting [Medical Device Reporting (MDR)] to FDA under part 803 or 804 of this chapter shall automatically consider the report a complaint and shall process it in accordance with the requirements of 820.198.

Section 820.198(d) requires that any complaint that represents an event which must be reported to FDA under part 803 or 804 of this chapter shall be promptly reviewed, evaluated, and investigated by a designated individual(s) and shall be maintained in a separate portion of the complaint files or otherwise clearly identified. In addition to the information required by 820.198(e), records of investigation under this paragraph shall include a determination of:

(1) whether the device failed to meet specifications;
(2) whether the device was being used for treatment or diagnosis; and
(3) the relationship, if any, of the device to the reported incident or adverse event.

Because of the MDR and complaint relationship, manufacturers should have the service personnel collect as much as is possible of the information required to complete the records of investigation, steps 1 - 3 listed above. Thus, the service form for some devices may need blanks/areas to support the collection of the needed information.

The service requirements AND complaint requirements shall be met for such combination service/MDR/complaint events. If the death or serious injury was caused by a design error, it may not be possible to perform a repair.

CORRECTIVE AND PREVENTIVE ACTION

A major intent of the service requirements is to look for quality problems during servicing and analysis of service data, and, if problems are found that affect or could affect safety or performance, to mandate appropriate corrective action. Thus, the collection (820.200) and analysis (820.100) of servicing data are required and these are part of the quality feedback system. Without the feedback provided by the quality audit and other information sources, such as complaints and service records, manufacturers operate in an open loop system with no assurance that the process used to design and produce devices is operating in a state of control.

Section 820.100, Corrective and Preventive Action, requires the analysis of quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems.

In-warranty or out-of-warranty are not factors to be considered when collecting or analyzing data regarding servicing.

When nonconformities are found they are to be investigated to determine the cause, such as an inadequate quality system or a defect in the design, component(s), assembly, processing, labeling, packaging, installation method, service technique, etc.

The collection and analysis of service data should be broad based because the root cause may be: an inappropriate component; a bad component; early wear out; poor maintenance; compatibility; human factors, and safety; misuse; misuse due to inadequate labeling; poor workmanship; incorrect assembly; etc.

The investigation and corrective actions should continue until valid actions are identified and implemented to correct and prevent recurrence of nonconforming product and other quality problems.

If service instructions, techniques, equipment, etc., contribute to a quality problem, make a quality problem worse, destroy valuable data, etc., then such items are also subject to investigation and corrective action.

EXHIBIT

An example of a service request form is included in this chapter. This form may be modified to match individual needs as appropriate.

CUSTOMER SERVICE REQUEST	**Service Report No.:**
Device Name:	
ID/Cat. No.:	**Lot Number:**
Any Specific Rev/Mod. #:	**Date placed in use:**
Manufacturer/Distributor:	
Account Name:	
Account Address:	
Phone Number:	**Fax Number:**
Last Service Report (optional):	**Date Of Last Service:**
Last service comments:	
Technician:	**Date:**
Device Location:	
Customer Description Of Device Problem:	
Were you told that there was a serious injury or death associated with this problem? **NO __ YES __ If yes, describe relationship to incident or event.** **Was device being used for treatment or diagnosis?**	
Describe any unusual environment:	
Describe any evidence of misuse:	
If a repair, device problem(s) you found:	
Maintenance and/or repairs performed:	
Service Completed:	**Service not completed:** _____
Reason Not Completed:	

CUSTOMER SERVICE REQUEST	
In charts below, write identification code of components replaced. Write in first letter of ID code where necessary. Be SURE to put drawing number & rev. level in top row.	

Drawing number that shows replaced components listed below: .....rev.			
CAP	**CAP**	**CAP**	**CAP**
RES	**RES**	**RES**	**RES**
IC	**IC**	**IC**	**IC**
TRANSISTOR	**TRANSISTOR**	**TRANSISTOR**	**TRANSISTOR**
DIODE	**DIODE**	**DIODE**	**DIODE**
BAT	**LED**	**COIL**	**COIL**
FUSE	**FUSE**	**LAMP**	**LAMP**
CABLE	**CABLE**	**DET**	**DET**

Drawing number that shows replaced components listed below: .....rev.			
CAP	**CAP**	**CAP**	**CAP**
RES	**RES**	**RES**	**RES**
IC	**IC**	**IC**	**IC**
TRANSISTOR	**TRANSISTOR**	**TRANSISTOR**	**TRANSISTOR**
DIODE	**DIODE**	**DIODE**	**DIODE**
BAT	**LED**	**COIL**	**COIL**
FUSE	**FUSE**	**LAMP**	**LAMP**
CABLE	**CABLE**	**DET**	**DET**

Drawing number that shows replaced components listed below: .....rev.			
CAP	**CAP**	**CAP**	**CAP**
RES	**RES**	**RES**	**RES**
IC	**IC**	**IC**	**IC**
TRANSISTOR	**TRANSISTOR**	**TRANSISTOR**	**TRANSISTOR**
DIODE	**DIODE**	**DIODE**	**DIODE**
BAT	**LED**	**COIL**	**COIL**
FUSE	**FUSE**	**LAMP**	**LAMP**
CABLE	**CABLE**	**DET**	**DET**

17 QUALITY SYSTEM AUDITS

INTRODUCTION

Section 820.20 outlines the quality system requirements of the Quality System (QS) regulation. As discussed in Chapter 2, every quality system should include: management policies; objectives; an organization; documentation; performance of tasks according to policies; monitoring of the system (feedback) and corrective action as indicated by the feedback. Section 820.22 requires that the quality system be monitored through audits. The analysis and use of feedback data from product acceptance, audits, complaints, repairs, and other sources are necessary parts of a self correcting quality system. Thus, the audit of a quality system is one of the most important GMP requirements. The quality system first implemented by a new manufacturer will change as the manufacturer grows and as the company's products, operations and employees change. Therefore, a quality system should change with the company. Quality system audits are the primary tool for assuring that the quality system changes are correct and are correctly implemented.

A quality audit is a documented independent inspection and review of a quality system. The audit is performed on a periodic basis in accordance with written procedures. The objective is to verify, by examination and evaluation of objective evidence, the actual degree of compliance with those elements of the quality system under review. These audits are an essential part of every medical device manufacturer's effort to assure safe and effective devices. Regardless of how well a quality system is planned, monitoring of the system is required if the quality system program is to be effective in assuring that finished devices meet specifications. FDA analysis of factory inspections has shown that manufacturers who do not have an adequate quality audit system usually do not have an adequate quality system. An evaluation of approximately 2400 manufacturers that had received GMP inspections by FDA showed that manufacturers with an adequate quality audit system were in compliance with approximately 96 percent of the GMP requirements, while those that did not have an adequate audit system were in compliance with approximately 70 percent of the requirements.

If conducted properly, a quality audit can detect quality system defects. Isolation of unsatisfactory trends and correction of factors that cause defective products prevent the production of unsafe or nonconforming devices. Without an effective quality audit function, the quality system program is incomplete -- there is no assurance that a manufacturer is consistently in a state-of-

control. In addition, the proper implementation of a quality audit system can result in cost savings by identifying and correcting problem areas. Without an audit, the quality system becomes an open loop without feedback to management and without corrective action. Without overt management support, the quality system program will eventually become ineffective and, as history has shown, ignored.

AUDIT REQUIREMENTS

The QS regulation requires that planned and periodic audits of the quality system shall be performed to verify compliance with the quality system requirements. The audits are to be performed in accordance with written procedures by appropriately trained individuals who do not have direct responsibility for the matters being audited. Audit results shall be documented in written audit reports, which shall be reviewed by management personnel, who have responsibility for the matters audited, and by other involved parties. Follow-up corrective action, including re-audit of deficient matters, shall be taken when indicated. Upon request of a designated FDA employee, an employee in management with executive responsibility shall certify in writing that the audits have been performed and documented, the dates on which they were performed, and that any required corrective action has been undertaken.

To assure that company quality goals will be routinely met and to comply with the QS regulation, quality system audits should:

- **measure the effectiveness of the quality system;**
- **provide objective evidence that adequate controls are in place; and**
- **assure that products and processes conform with specifications.**

Where practical, manufacturers should include audits of their suppliers, calibration laboratories, and contractors as part of a quality system audit. Manufacturers should audit suppliers where needed, to assure that they have adequate quality system controls for raw materials and components shipped to and received by the manufacturers under supplier certification or certificate of compliance with specifications. An example of a detailed supplier (vendor) survey (audit checklist) form is in the Exhibits.

Procedure

All manufacturers should have a written quality audit procedure, although the details will vary with the manufacturer size and nature of the manufacturing operations. An audit procedure should include:

- **an objective,**
- **audit scope,**
- **an audit schedule,**
- **assignment of responsibilities,**
- **evaluation criteria,**
- **management review of results, and**
- **corrective action policies, schedules, etc.**

Before writing their audit procedure, some manufacturers may find it helpful to rearrange the key GMP requirements for an audit in a structured format as shown below:

- **Who? Designee(s)**
- **What? Quality system**
- **When? X months**
- **How? Per checklist**
- **Results? Report/review**
- **Actions? Corrective**

This structured format helps lead auditors into covering key requirements in the audit procedure and "getting straight to the point when writing procedures." Thus, this format tends to reduce the length and increase the clarity of audit procedures.

Formal procedures should start with an objective. In this case, the audit objective was discussed in the opening paragraphs of this chapter -- to monitor the quality system and take any needed corrective action. The audit scope should include all functions that impact on whether devices will meet specifications. These functions include personnel training, facilities, environment, design controls, device master and history records, equipment calibration, suppliers, label control, process controls and validation, complaint files, data feedback, preparation for FDA GMP inspections, etc. Manufacturers that have a total quality system composed of a design quality system and a manufacturing quality system should audit the entire system; otherwise, it is no longer a total quality system! Audits should cover all buildings and operations as necessary to make certain that the desired or required quality system is properly implemented.

The quality system audit required by the QS regulation is not intended to be a product audit. However, the adequacy of procedures used to determine product acceptability should be audited periodically. Product audits and review of the device master record are desirable as independent evaluations of product quality to determine the product's fitness for use and conformance to specification and, these may be acceptable in satisfying most quality audit requirements when product and process are very simple and the operation is small. As products and processes become more complex, evidence from inspection and testing of products no longer provides full assurance that the manufacturing system will consistently produce quality products. Instead, full quality system audits are required to make certain that:

- **the established quality system is adequate for producing devices that consistently meet the device master record requirements,**
- **all system requirements are being met, and**
- **the system will continue to function when new products are introduced, changes are made, the workforce is understaffed, and the manager is on vacation.**

Audit Schedule

Manufacturers are responsible for deciding the frequency of audits. The frequency should depend upon previous audit findings, any indications of problems, and known stability of the manufacturing process. If an audit reveals no problems, the audit intervals could be lengthened -- if problems are identified, audits may need to be conducted more often. Audits are usually conducted every 6 to 12 months, but should not exceed 12 months. Some companies split their audit into parts, and perform one or more parts per month or quarter, or audit one or more operations per month or quarter. This approach is valuable because it tends to direct attention toward problems that can be

resolved within reasonable time limits and existing budgets. However, such segmented audits may fail to identify company-wide problems. Thus, reviewers of segmented audit reports should look for indications of company-wide problems.

Independent Auditor

The QS regulation (820.22) requires that quality system audits be conducted by individuals not having direct responsibility for the matters being audited. This requirement may be satisfied by an audit team consisting of persons representing product development and manufacturing. Then, when the product development area is being audited, the manufacturing persons should have the lead responsibility and vice versa. For any element of the quality system being audited, at least one member of the team should not have direct responsibility for the element being audited. Management should designate one member as the team leader for a given audit in order to support consistency, timeliness, completeness, and uniform response. Of course, a consultant, corporate, or other independent auditor may be used.

The requirement for an independent audit should generally be met; however, if a very small manufacturer, particularly one in which everyone is directly involved in daily design and production activities, concludes that independent audits would be unduly burdensome or impractical, the requirement for independence may be waived. However, if FDA finds, as a result of inspection or other means, this waiver has compromised the quality system, FDA may require an independent audit, increase the frequency of FDA GMP inspections, or take other appropriate regulatory action.

Employee Training

Individual(s) responsible for conducting audits should be sufficiently trained and experienced to detect variations and problems in the quality system [820.20(b), 820.22]. An auditor is expected to objectively compare existing employee training, design controls, manufacturing processes, facilities, environmental control, records, test/inspection activities, label control systems, feedback, etc., against what they should be. To do this, the individual(s) should have a working knowledge of:

- **how products are developed and validated,**
- **how the device(s) is made,**
- **the manufacturing processes and process controls,**
- **how changes are controlled,**
- **quality assurance principles that apply, and**
- **the human relations aspect of auditing.**

As with any GMP training, a record shall be maintained of the audit training given each employee.

Because the quality system requires a written audit report, auditors should have sufficient writing skills to effectively communicate findings and recommendations. The effectiveness of the audit begins with the planning. The manufacturer should start by defining the purpose and scope of their audit keeping in mind their quality systems requirements. An audit team leader and the other members of this team should be identified early in the planning process. The members of this team should possess skill and knowledge of quality system principles. Preparing an audit checklist will enable the team to properly cover the quality system requirements. Review of previous audits and their resulting reports is an excellent way for the audit team to correctly evaluate their quality

system audit program. The background preparation should also include becoming familiar with company policies, operations, and products. The audit team should notify the parties they will audit and also hold a pre-audit conference among the audit team members to clarify exactly what the audit will include and what the objective(s) of their audit will be. Thus, preparing for an audit should include elements such as:

- **selecting a knowledgeable audit team,**
- **preparing an audit checklist,**
- **developing a planned and systematic procedure,**
- **structuring the audit to determine both positive and negative trends, and**
- **structuring the audit and report to promote follow-up actions.**

Evaluation Criteria

Each manufacturer shall determine the criteria to be used for conducting the audit. In general, medium to large manufacturers will need extensive documentation outlining the areas to be audited and the acceptable criteria for each of these areas. The GMP requirements are a baseline for the evaluation criteria; however, because the QS regulation is broad, each manufacturer shall tailor the criteria to the design and manufacturing operations they are actually performing. Small manufacturers may need only minimal documentation, and this may consist of an audit checklist with appropriate ancillary instructions to assure that all aspects of the quality system are covered.

An audit checklist may be a series of questions, phrases, trigger words, or any combination of these that will prompt auditors to cover the entire quality system. Checklists should cover requirements of the QS regulation applicable to company products, operations, and other areas company management has decided are included in their total quality system. If operations or devices change, evaluation criteria and checklists shall be appropriately updated.

Results and Corrective Actions

A quality system audit program that has been established in accordance with the QS regulation and implemented in sufficient depth can detect undesirable variations and trends in operating procedures. Management awareness of these undesirable variations should lead to corrections and help prevent the design and production of unsafe, unreliable, or ineffective devices.

The QS regulation requires follow-up corrective action, including re-audit. When indicated, audit results shall be given to individuals responsible for each of the operations audited, especially if deficiencies are found. Audit results shall be reviewed by all key management personnel, especially those responsible for the matters audited.

An audit should never be used as a disciplinary tool. This use will lead to ineffective audits because employees may become reluctant to reveal any possible problems for fear of retribution.

Audit Certification

Under 704(e) of the FD and C Act FDA has authority to review and copy all records required by the QS regulation; however, FDA has elected not to review audit reports. The exception [820.180(c)] to FDA's policy of not seeking access to reports of audits of quality systems is that FDA may seek production of these reports in litigation under applicable procedural rules, along with other

confidential documents. Thus, a copy of the current audit report should be maintained by the manufacturer. FDA policy was established because the agency does not wish to prejudice audits by having auditors concerned that their comments will be reviewed by FDA investigators. Although FDA investigators do not have routine access to audit reports, they can request manufacturers to certify that audits have been conducted and the results documented; however, investigators do not routinely request certification. If requested, an employee in management with executive responsibility should certify, in writing, that the manufacturer has complied with the audit requirements of the QS regulation.

Investigators usually will ask questions regarding the audit report such as:

- **who prepared the report;**
- **what does the quality system audit include;**
- **when was the report written;**
- **using the checklist how should the audit be conducted;**
- **who reviewed the information and wrote the report; and**
- **were corrective action and re-audit(s) taken based on the audit result.**

If investigators suspect audits are not being conducted, questions to determine consistency in answers may be addressed to those individuals who should have reviewed these reports. FDA investigators will routinely review audit procedures and audit checklists.

EXHIBITS

Two examples of audit procedures with checklists are included in this chapter. These may be modified to match individual operations as appropriate or used as guidances.

Policy/Procedure for Quality System Audit

In response to requests by small manufacturers, DSMA developed this procedure as an example of a minimum procedure for quality system audits. Following the procedure are comments to aid small manufacturers in completing the procedure and developing a checklist that should be used with it.

No details are given for the format of the audit "report" because the format generally is not important for the small manufacturer -- employees of small manufacturers communicate daily with each other. In fact, the "report" may be the list of findings neatly noted on the audit checklist. As noted in the procedure, however, summaries of the audit findings and corrective actions are recommended. The format Who, When, etc. discussed in the text, was used to develop this example procedure. The first three items in this format are reflected in item 1 of the example and the remaining three are reflected in items 2, 3 and 4 of the example. The scope encompasses the entire quality system.

Quality System Audit Procedure

Quality System Audit Procedure is an audit procedure that can be used by a medium to large manufacturer. In comparison to the small company, there are more people on the audit team, more audits per year, and the reports are distributed to more managers, some of which may be at corporate headquarters. Therefore, this procedure contains more details than the one suggested for the small company. For example, the procedure dictates the format of the audit report for the benefit of the managers, who may review reports for many different operations per year.

Vendor Survey Form

The vendor survey form is applicable to a vendor or contractor or may be modified and used as an internal audit checklist. This survey form is divided into areas of concern such as raw material and component control, manufacturing, quality control/assurance, etc. Also, it is a more conventional checklist with places to check off answers to the questions. This form includes a header with space for manufacturer name, address, date prepared, etc., and general information about the manufacturer such as, annual sales, years in business, other plant locations, etc. Your manufacturers can look at these two styles of checklists and decide to use one or the other, a combination of both, or a totally different format.

Title: POLICY/PROCEDURE FOR QUALITY SYSTEM AUDIT No._____Rev._____

Approved by_____Date_____

1. **A general audit of the entire quality system shall be performed by_____ every_____ months (an audit team may be used).**

2. **The latest company approved audit checklist (number) _____shall be used. The audit checklist shall be updated as required and approved by _____to reflect our current quality system needs.**

3. **The completed checklist and audit results summary report shall be reviewed with the following managers, as appropriate, who are responsible for the matters audited: _____, _____and_____ . Minutes of the review meeting, including a list of attendees and desired corrective actions, shall be taken, distributed and filed by_____ . This same procedure shall be used when reviewing the findings of GMP inspections by FDA investigators. (820.20)**

4. **Corrective actions shall be taken by all affected persons as discussed in the review meeting. _____ will coordinate the corrective actions, re-audits, and keep management informed. A summary report of the status of the corrective actions, as determined by a re-audit of the affected areas or other appropriate means, will be written by _____ and filed with the original audit report. The status report shall be updated at least bimonthly if there are any uncompleted corrective actions.**

*** * * * * * * * * ***

Comments on the Policy/Procedure

A. ”Rev." is the revision level of the latest company approved procedure.

B. The above blanks should be completed with employee position titles and, if desired, employee names.

C. An audit checklist may be a detailed series of questions, phrases, trigger words or any combination of these to assure that the auditor covers the entire quality system. The checklist should cover the requirements of the QS regulation applicable to each company's products and operations plus other areas that company management had decided are included in the total quality system. A suggested way to develop a question-type checklist is to refer to the table of contents of the QS regulation and the chapters of this manual. Then generate questions for each topic as applicable to specific products and operations of the manufacturer. If operations or devices change, the checklist should be updated. A small portion of a quality audit checklist follows.

A few cites are given. There are more. For example most of the QS regulation applies to labeling -- not just 820.120.

SPECIFICATION CONTROLS (820.30, .40, and .181)	YES	NO	COMMENTS
1. Is an adequate system in place to control all engineering drawings, specifications and other related documentation?			
2. Does the system require adequate review, and approval of all new documentation and changes to documents?			
3. Does the system require controlled, timely distribution of new specifications and specification changes?			
4. Are procedures provided and adequately implemented to assure collection of obsolete documentation?			
5. Are all specifications used in production approved, dated, and current?			
6. Etc.			

PROCESS CONTROLS (820.70, .40, .60 and .80, .86)	**YES**	**NO**	**COMMENTS**
1. Are current, approved process specifications/procedures such as work instruction, etc., used to define each process?			
2. Are process changes made according to a formal change system and documented?			
3. Are process changes communicated in a timely manner?			
4. Do process specifications and procedures properly reflect the work to be accomplished?			
5. Are adequate acceptance and rejection criteria provided for the output of each process?			
6. Are in-process and rejected items adequately identified and/or segregated to prevent mix-ups?			
7. Etc.			

PERSONNEL 820.20(b)(2), 820.25, and 820.70(d)	**YES**	**NO**	**COMMENTS**
1. Are there sufficient personnel having the necessary education, background, training, and experience to assure that all design and manufacturing operations are correctly performed?			
2. Are training programs conducted and documented? Is the program proactive? Do design personnel have basic training in safety, use of standards, labeling, and applicable regulations?			
3. Are all employees made aware of device defects which may occur from the improper performance of their specific jobs?			
4. Are all employees including salespersons made aware that they must report all complaints received from any source to the company complaint department?			
5. Are quality system personnel made aware of defects and errors likely to be encountered as part of their individual quality system function?			
6. Are verification/validation personnel made aware of design errors that may be found?			
7. Are personnel in contact with the device or its environment appropriately: **a. clean?** **b. healthy?** **c. attired?**			
8. Etc.			

QUALITY ASSURANCE FUNCTIONS	**YES**	**NO**	**COMMENTS**

1. Does the quality assurance unit or qualified designee do the following?
- **a. review customer purchase orders**
- **b. approve or reject components**
- **c. approve or reject manufacturing materials**
- **d. approve or reject in-process materials**
- **e. approve or reject packaging materials**
- **f. approve or reject labeling**
- **g. approve or reject finished devices**
- **h. approve or reject devices manufactured by another company**
- **i. review production records**
- **j. approve or reject devices processed by another company**
- **k. approve or reject devices packaged by another company**
- **l. approve or reject devices held under contract by another company**
- **m. help provide solutions for quality system problems**
- **n. verify implementation of solutions for quality system problems**
- **o. assure that all quality system checks are appropriate and adequate**
- **p. assure that all quality system checks are performed correctly**

2. Are periodic audits of the quality system conducted to verify compliance with quality system program requirements?

3. Are audits of the quality system program:
- **a. performed in accordance with written procedures?**
- **b. conducted by appropriately trained individuals?**
- **c. conducted by individuals who do not have direct responsibility for matters being audited?**

4. Are audit results:
- **a. documented in written audit reports?**

QUALITY ASSURANCE FUNCTIONS	**YES**	**NO**	**COMMENTS**

b. reviewed by management having responsibility for the matters audited?

5. Does company have a copy of the last audit report on file?

6. Is follow-up corrective action, including re-audit of deficient areas, taken when indicated?

7. Etc.

QUALITY SYSTEM AUDIT PROCEDURE

No._____ Rev._____ Approved_____ Date _____
ECN History_____

POLICY: Periodic and planned audits of systems, training documentation processes, product flow and feedback shall be performed to assure compliance with regulatory and company requirements for current Good Manufacturing Practices (quality system).

SCOPE: All facilities, design activities, manufacturing operations, and product lines.

PROCEDURAL GUIDE: An audit of design activities shall be done annually. Routine quality audits of selected production areas shall be conducted each month. The entire operation shall be covered during a 12-month cycle. An area may be audited more than once. An "Action Audit" for any area or element may be initiated by the Manager of Quality Assurance at any time if a special problem arises.

The teamwork approach shall be used to identify and correct deficiencies.

The audit team shall consist of the Senior Quality Auditor (team leader) plus one or more individuals from other disciplines who have no direct responsibility for the area being audited. A team auditing an Operations unit should include an R&D representative. A team auditing a quality systems unit should include an Operations representative. An audit of design activities shall include a representative from both the regulatory and the manufacturing divisions.

The Manager of Quality Assurance selects the team member in consultation with the Department Managers.

A. AUDIT PREPARATION - The Quality Auditor (team leader) reviews applicable change control records subsequent to a design transfer, any FDA clearance delay information, recall records, standard manufacturing procedures, device histories, complaint history, device labels and inserts, previous audits with results, follow-up audits, plus any other document relative to the audit.

B. AUDIT INITIATION - The Quality Auditor prepares/updates an audit checklist for systematic examination of the area to be audited, informs the Manager of the department being audited at the start of the audit, and reviews observations with the Department Manager.

C. AUDIT ANALYSIS - The Quality Auditor reviews the data gathered, verifies important details, and writes an audit report according to the format delineated in the attached audit report outline.

D. ISSUANCE OF AUDIT REPORT - The Quality Auditor issues the written audit report to the President and Department managers within three working days following completion of the audit. If conditions are critical, the Director of Quality Assurance shall verbally brief appropriate staff members within 12 hours following audit completion. Audit reports shall be stamped "Confidential".

E. CORRECTIVE ACTION - The appropriate Management staff member shall be responsible for developing a schedule for correcting deficiencies cited in the audit report and submitting same within five working days to the Quality Assurance Manager. Included in the correction schedule shall be the responsible individual, and the date when corrective action will be completed. The Manager of Quality Assurance shall act as arbiter, if necessary, to judge validity of the deficiency, responsible individual, and reasonable date to complete the corrective action.

F. AUDIT FOLLOW-UP - The Quality Auditor maintains a log listing deficiencies, responsible individual, target date for corrective action, and actual date of correction. If the same deficiency occurs on a second follow-up audit, the President shall be notified in writing by the Quality Assurance Manager.

G. LOG OF AUDITS AND FOLLOW-UP AUDITS - The master log shall be maintained by the Senior Quality Auditor. The audit log file shall include a copy of current audits, list of areas to be audited during the 12-month period, and list of areas audited to date (i.e., part of the Master Log).

H. REPORT NUMBERS - Audit numbers shall be composed of the date followed by the sequential number of the audit being reported (e.g., 98-4 for the 4th audit during 1998).

AUDIT REPORT COVER DATA
Area Audited _____ Audit No._____ Date: _____

Audit Team members_____
_____

Sr. Auditor's Signature: _____ (Team Leader)

REPORT OUTLINE

1. **PURPOSE AND AREA DESCRIPTION - Describe initiating factors for the audit, limitations of audit, and area being audited.**

2. **MAJOR FACTS - Summarize for management review the most undesirable conditions and practices in order of their relative importance.**

3. OBSERVATIONS AND FACTUAL DETAILS - Give a detailed account of the current

practices and the deficiencies listed in four below.

4. DEFICIENCIES - List deficiencies in procedures, standards, documentation, safety, etc., along with identity of relevant regulation, SMP, SOP, etc.

5. FOLLOW-UP - State plans for follow-up review to establish individual responsibilities and completion dates.

Form No. XXX
7-78

VENDOR SURVEY FORM

DATE PREPARED _____

COMPANY SURVEYED		
ADDRESS		
CITY	STATE	ZIP CODE
TELEPHONE NO. ( )	TELEX	

NOTICE:

I (We) certify that the information contained in the attached survey form is accurate and complete as of the date indicated. Where trade secret or other proprietary information is involved, the person interviewed has marked those responses not verified by the interviewer. All information obtained will be kept confidential. A corporate officer of the company surveyed will review all responses made at the time of survey. This survey has been made with the permission of the company surveyed.

SIGNATURE	TITLE	LOCATION
SIGNATURE	TITLE	LOCATION
SIGNATURE	TITLE	LOCATION

PART I — GENERAL INFORMATION

ANNUAL SALES	YEARS IN BUSINESS	PRIVATELY OWNED	SUBSIDIARY, DIVISION, FACILITY OF

OTHER PLANT LOCATIONS _____

LIST MAJOR CUSTOMERS _____ TYPE OF CONTRACT _____

NOT AVAILABLE ☐ NOT AVAILABLE ☐

LIST COMPANY MANAGEMENT

NAME	TITLE	INTERVIEWED

PRODUCTS FOR WHICH SURVEY WAS PERFORMED (ATTACH LABELING) _____

TOTAL NUMBER EMPLOYEES _____ LABOR RATIO OF SUPERVISORS _____ TO PRODUCTION PERSONNEL _____

WORK SCHEDULE HOURS _____ NUMBER SHIFTS _____ DAYS PER WEEK _____

ARE TRAINING PROGRAMS FOR PERSONNEL UTILIZED Yes☐ No☐

FACILITY

NUMBER BUILDINGS ON SITE _____ TYPE (SINGLE/MULTISTORY; WOOD/BRICK/BLOCK/STEEL) _____

LOCATION IN INDUSTRIAL PARK☐ URBAN☐ SUBURBAN☐ RURAL☐ EQUIPMENT OWNED OR LEASED _____

SQUARE FOOTAGE IN MANUFACTURING _____ ADMINISTRATION _____ STORAGE _____ ENGINEERING, R&D _____

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LIST PROCESS CAPABILITIES AND SPECIAL MANUFACTURING EQUIPMENT ESSENTIAL TO MATERIALS BEING PROCURED.

1. _____
2. _____
3. _____
4. _____
5. _____

LIST MANUFACTURING DONE BY OUTSIDE SOURCES (SUBASSEMBLY, PACKAGING, KIT ASSEMBLY, ETC.)

1. _____
2. _____
3. _____
4. _____
5. _____

IS THERE A DOCUMENT/PROCESS FLOW MANUAL OUTLINING ALL MANUFACTURING STEPS, RECORDS, AND CONTROLS FROM RAW MATERIALS TO FINISHED PRODUCT (AS REQUIRED FOR SOME GOVERNMENT CONTRACTS) Yes☐ No☐

DOES THE MANUFACTURER HAVE LIABILITY INSURANCE Yes☐ No☐

INSURED BY _____

HAS THE MANUFACTURER BEEN INSPECTED BY ANY STATE OR FEDERAL AGENCIES WITHIN THE LAST TWO YEARS Yes☐ No☐

NAME OF AGENCIES

WERE RECALLS INVOLVED Yes☐ No☐

COMMENTS _____

PART II — RAW MATERIALS AND COMPONENTS CONTROL

PURCHASING

IS QUALIFICATION BASED ON WRITTEN SPECIFICATIONS, AND APPROVAL OF VENDOR SOURCES Yes☐ No☐

ARE REJECT/ACCEPT LIMITS SHOWN Yes☐ No☐

IS APPROVAL BASED ON

QUALITY HISTORY CARDS☐ SUPPLIERS CERTIFICATE☐ ON SITE SURVEY☐ OWN QC TESTING☐

OTHER _____

ARE SPECIFICATION CHANGES REVIEWED AND SIGNED OFF BY QC PERSONNEL Yes☐ No☐

TESTING

ARE WRITTEN TEST PROCEDURES IN USE Yes☐ No☐

TEST RESULTS ON FILE Yes☐ No☐

SAMPLING PLAN USED 100%☐ MIL SPEC☐ AQL☐ RANDOM☐

OTHER _____

DO TEST RESULTS INDICATE QUANTITY SAMPLED☐ METHOD OF ANALYSIS☐ DATE & SIGNATURE OF ANALYST☐ SAMPLE TRACEABILITY☐

IS THERE A RETENTION SAMPLE SYSTEM FOR RAW MATERIALS/COMPONENTS Yes☐ No☐

IN PLANT CONTROL

MATERIAL ASSIGNED ALPHA-NUMERIC OR IDENTIFYING MARK FOR EACH INCOMING LOT Yes☐ No☐

MATERIAL VISIBLY MARKED AS

SAMPLED☐ APPROVED☐ REJECTED☐ NOT MARKED☐

INVENTORY LOG OR RECORD KEPT	Yes☐	No☐
STORAGE AREA SEPARATE	Yes☐	No☐
SEGREGATED WITHIN STORAGE AREA	Yes☐	No☐
STOCK ROTATION (FIFO) SYSTEM USED	Yes☐	No☐
AUTHORIZED CUSTODIAN CONTROL	Yes☐	No☐
GENERAL HOUSEKEEPING NEAT AND ORDERLY	Yes☐	No☐

REJECTED MATERIALS ARE:

CLEARLY IDENTIFIED	Yes☐	No☐
PHYSICALLY SEGREGATED	Yes☐	No☐

PART III — MANUFACTURING

MASTER PRODUCTION RECORDS

IS THERE A SINGLE CONTROLLED FILE OF MASTER RECORDS FOR EACH PRODUCT Yes☐ No☐

BATCH SHEETS☐ LINE ENGINEERING, ASSEMBLY DRAWINGS☐

OTHER _____

ARE THESE MASTER RECORDS SIGNED AND DATED Yes☐ No☐

DOUBLE SIGNATURE☐ REVISION DATES☐

ARE THE PROCESS, ASSEMBLY, OR MANUFACTURING STEPS FULLY DESCRIBED:

IN THE MASTER PRODUCTION RECORD	Yes☐	No☐
IN A SEPARATE DOCUMENT OR RECORD	Yes☐	No☐

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IS THERE A MASTER DOCUMENT TO INDICATE:

QC POINTS FOR IN-PROCESS MANUFACTURING — Yes☐ No☐
TYPE OF TEST OR INSPECTION TO BE MADE — Yes☐ No☐
METHOD OF MEASUREMENT — Yes☐ No☐
WHO PERFORMS TEST OR INSPECTION — Yes☐ No☐
LEVEL OF ACCEPT/REJECT (LIMITS) — Yes☐ No☐
FOR MANUFACTURING, PROCESSING, SUBASSEMBLY, OR PACKAGING DONE BY OUTSIDE SOURCES, ARE THERE.
MASTER PRODUCTION RECORDS — Yes☐ No☐
QC SPECIFICATIONS AND METHODS RECORDS — Yes☐ No☐
OUTSIDE SOURCES NOT USED — Yes☐ No☐

PRODUCTION AREA

IS THE WORK FLOW ORGANIZED — Yes☐ No☐
DISTINCT STAGING AREA FOR RAW MATERIALS OR COMPONENTS USED IN MANUFACTURING — Yes☐ No☐
PRODUCTION OR ASSEMBLY LINES SEGREGATED — Yes☐ No☐
GENERAL HOUSEKEEPING AND ENVIRONMENTAL FACTORS GOOD — Yes☐ No☐
WRITTEN PROCEDURES FOR PLANT SANITATION AVAILABLE — Yes☐ No☐

PRODUCTION EQUIPMENT

MAINTENANCE OR SERVICE RECORDS AVAILABLE — Yes☐ No☐
CALIBRATION RECORDS KEPT ON PERIODIC BASIS — Yes☐ No☐
MEANS OF READILY IDENTIFYING TYPE AND STAGE OF PROCESSING BEING DONE ON THE EQUIPMENT — Yes☐ No☐

PRODUCTION RECORDS

ARE PRODUCTION DOCUMENTS COLLECTED AND FILED — Yes☐ No☐
KEPT _____(YEARS)

COMPLETE HISTORY☐ LABELING SAMPLES INCLUDED☐ TRACEABILITY BY LOT OR SERIAL NUMBER☐
PARTIAL HISTORY☐

PACKAGING

ARE FINISHED GOODS PACKAGING OPERATIONS SEGREGATED — Yes☐ No☐
UNDER SUPERVISED CONTROL — Yes☐ No☐
LABEL RECORDS KEPT — Yes☐ No☐

PRE-LABEL COUNT☐ RECONCILIATION☐

ARE FINISHED GOODS PROPERLY IDENTIFIED, LABELED, AND STORED — Yes☐ No☐

PRIOR TO RELEASE☐ AFTER RELEASE☐

REJECTED MATERIALS

ARE THERE WRITTEN PROCEDURES FOR DISPOSING OF OR REWORKING REJECTED ITEMS — Yes☐ No☐
ARE REJECTED PRODUCTS HELD IN QUARANTINE PENDING FINAL DISPOSAL — Yes☐ No☐

SEGREGATED AREA☐ SPECIAL MARKINGS☐

RETENTION SAMPLES

ARE SAMPLES OF FINISHED GOODS RETAINED — Yes☐ No☐
FROM EACH PRODUCTION RUN☐
IN A SEPARATE CONTROLLED AREA☐
IN THE SAME CONTAINER/CLOSURE SYSTEM IN WHICH THEY ARE SOLD☐
IN CONTAINERS DIFFERENT FROM UNIT AS SOLD☐
KEPT FOR A PERIOD OF _____(YEARS)
WRITTEN LOG OR FILE☐

STERILE COMPONENTS *(IF APPLICABLE)*

ARE THERE PROCEDURES FOR ESTABLISHING AND MAINTAINING ASEPTIC CONDITIONS — Yes☐ No☐
ARE METHODS FOR ROUTINE AUDITING OF STERILE AREAS USED — Yes☐ No☐
ARE THERE PROCEDURES FOR WORKING IN STERILE AREAS — Yes☐ No☐
FOR CLEANING AND STERILIZATION OF EQUIPMENT — Yes☐ No☐
FOR BULK AND FINAL PRODUCT STERILITY TESTING — Yes☐ No☐
IS PROCESS STERILITY FOR EACH RUN DOCUMENTED IN THE PRODUCTION RECORDS — Yes☐ No☐

STERILE PROCESS USED

ETO☐ RADIATION☐ STEAM☐ FILTRATION☐
CHEMICAL☐ OTHER _____

PART IV — QUALITY CONTROL/ASSURANCE

ORGANIZATION AND FUNCTION

DOES THE QUALITY CONTROL-INSPECTION GROUP REPORT DIRECTLY TO THE TOP, INDEPENDENT OF PRODUCTION, MARKETING, OR OTHER ORGANIZATION GROUPS WITHIN THE MANUFACTURING COMPANY. (SEE COMPANY ORGANIZATION CHART) — Yes☐ No☐

DOES THE QUALITY CONTROL-INSPECTION GROUP HAVE FULL AUTHORITY TO WITHHOLD SHIPMENT OR FURTHER PRODUCTION OF REJECTED ITEMS — Yes☐ No☐

ARE THE QUALITY CONTROL PROCEDURES:
IN A FORMAL WRITTEN DOCUMENT — Yes☐ No☐
REVISED ON A PERIODIC BASIS — Yes☐ No☐

DOES THE QUALITY CONTROL/ASSURANCE-INSPECTION GROUP HAVE:
ADEQUATE EDUCATION, TRAINING OR EXPERIENCE — Yes☐ No☐

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UNDERSTANDING OF THEIR FUNCTION Yes☐ No☐ OTHER _____

OPERATIONS

ARE STAMPS, TAGS, MARKERS, ETC., USED TO VERIFY INSPECTION ACTIVITY Yes☐ No☐

ARE THE MARKINGS USED TRACEABLE TO AN INDIVIDUAL INSPECTOR Yes☐ No☐

ARE PRODUCTION SAMPLES FOR QC TESTING:

ADEQUATELY IDENTIFIED AS TO SOURCE Yes☐ No☐

RECORDED SOMEWHERE AT TIME OF SAMPLING Yes☐ No☐

ENTERED ON FILED TEST REPORT Yes☐ No☐

WRITTEN SAMPLING PLAN BASED ON.

100%☐ MIL SPEC☐ AQL☐ RANDOM☐

IS THE PRODUCT USED TESTED PRIOR TO FINAL RELEASE Yes☐ No☐

ARE OUTSIDE SOURCES USED FOR PRODUCTION TESTING Yes☐ No☐

UNDER FORMAL CONTRACT☐

USE TEST PROTOCOLS OR WRITTEN PROCEDURES☐

COPIES IN THE MANUFACTURING FILES☐

FACILITY REGISTERED OR LICENSED BY ANY FEDERAL, STATE OR PROFESSIONAL AGENCY☐

OUTSIDE TEST RESULTS FILED BY THE MANUFACTURER☐

IS THERE A FORMAL QUALITY ASSURANCE PROGRAM INVOLVING PERFORMANCE TESTING OF THE PRODUCT(s) AFTER RELEASE Yes☐ No☐

PART V — CUSTOMER COMPLAINTS AND RECALL CAPABILITIES

CUSTOMER COMPLAINTS

IS THERE AN ORGANIZED COMPLAINT FILE Yes☐ No☐

DOES EACH COMPLAINT STATE:

NATURE OF COMPLAINT☐

RESPONSE TO CUSTOMER (REPAIR, REFUND, REPLACE)☐

FURTHER CORRECTIVE/PREVENTIVE ACTION BY MANUFACTURER☐

COMPLAINT FILES KEPT FOR _____ (YEARS)

IS THERE A PERIODIC REVIEW OF COMPLAINT FILES FOR TRENDS Yes☐ No☐

IS THE REVIEW FILE AS A WRITTEN SUMMARY Yes☐ No☐

IS THERE A GROUP OR INDIVIDUAL ASSIGNED TO HANDLE CUSTOMER INQUIRIES AND FOLLOW UP ON COMPLAINTS Yes☐ No☐

ARE PRODUCT DEFECTS VERIFIED BY MANUFACTURER THROUGH TESTING Yes☐ No☐

WAS REVIEW OF COMPLAINT FILES FOR SURVEY PRODUCT MADE Yes☐ No☐

RECALL CAPABILITIES

IS THERE A COMPANY RECALL PLAN Yes☐ No☐

SHOWS HOW DECISIONS ARE MADE AND BY WHOM☐

HOW RECALL WILL BE ACCOMPLISHED☐

INSTRUCTIONS FOR RECOVERY AND ACCOUNTABILITY OF RECALLED PRODUCT☐

DO SHIPPING OR DISTRIBUTION RECORDS ON FILE SHOW:

CUSTOMER OR DISTRIBUTOR NAME AND ADDRESS Yes☐ No☐

DATE OF SHIPMENTS AND QUANTITY SHIPPED Yes☐ No☐

LOT OR SERIAL NUMBER OF PRODUCT SHIPPED Yes☐ No☐

DISTRIBUTION RECORDS ARE MAINTAINED _____ (YEARS)

DISTRIBUTION RECORDS ARE STORED AS:

COMPUTER LISTING☐

MICROFILM/MICROFICHE☐

MANUAL CARD/PAPER FILES☐

PART VI — REGULATORY COMPLIANCE

IS THE PLANT REGISTERED AS A DEVICE MANUFACTURER Yes☐ No☐

ARE THE SURVEY PRODUCT(S) LISTED WITH BUREAU OF MEDICAL DEVICES Yes☐ No☐

ARE ALL NECESSARY APPROVALS FOR MARKETING PRODUCTS AVAILABLE Yes☐ No☐

IS THERE A FILE WITH PAST AND CURRENT LABELING FOR EACH SURVEY PRODUCT Yes☐ No☐

IS THERE A FORMAL AUDITING PROGRAM OF THE QC OPERATION. IF SO, DONE BY WHOM Yes☐ No☐

LIST OF ATTACHMENTS AND COMMENTS

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18 FACTORY INSPECTIONS

INTRODUCTION

FDA determines compliance with the GMP requirements set forth in the Quality System (QS) regulation primarily by factory inspections. An FDA inspection of an establishment, however, can be initiated for a number of reasons. The reasons may be general, such as routine scheduling or a need to obtain data on industries new to FDA or, the reasons may be specific, such as investigation of a consumer or trade complaint, a product defect report, an adverse reaction, or a death. FDA also conducts inspections under the Compliance Status Information Systems (Com STAT) on behalf of the Veterans Administration (VA), Department of Defense (DOD), and Health Resources and Services Administration (HRSA). Upon arrival, the investigator presents his/her credentials and issues a Notice of Inspection form FDA 482. At the end of the inspection, observations are recorded on form FDA 483, List of Observations, and discussed with the manufacturer's management. Later the investigator will write an Establishment Inspection Report (EIR), which is a detailed record of the inspection and findings.

AUTHORITY AND COVERAGE

Section 704(a) of the Food, Drug, and Cosmetic (FD&C) Act gives FDA the authority to conduct GMP inspections of medical device manufacturers. During these inspections, facilities, manufacturing processes, records, and corrective action programs are examined by an FDA investigator. The results provide information necessary to evaluate a manufacturer's compliance with the device QS regulation (21 CFR 820).

Anyone who manufactures or stores a medical device can be inspected. A manufacturer is any person who designs, manufactures, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, relabeling, remanufacturing, repacking, or specification development, and initial distributor(s) of devices from foreign entities performing these functions.

Inspection Plan

This chapter offers ideas on ways that a manufacturer might prepare for, undergo, and respond to an FDA inspection. First and foremost, it is important to plan ahead! Before being visited by an FDA investigator, a manufacturer should have in place an inspection procedure which takes into account, and prepares a manufacturer for, any eventuality. It should detail company policy regarding an inspection and, very importantly, designate those individual(s) who will work with the FDA investigator. Try to anticipate situations and have written procedures covering them. These procedures will provide continuity from one inspection to another and help assure that corporate policies are followed by employees receiving and accompanying the investigator.

Each person designated as an FDA contact should be chosen carefully and be thoroughly familiar with the inspection procedure and company operations. An inspection will take longer if the contact person cannot answer questions without continually referring to the written procedures. The contact should be familiar with FDA regulations and practices and be able to anticipate problems or requests. FDA contacts be should knowledgeable about plant operations, and able to answer or obtain answers to the investigator's questions. Other individuals, with similar qualifications, should be designated to fill in during absences of the primary contact. A manufacturer might want secondary contacts to accompany the FDA investigator even when the primary contact is present in order for the secondary contact to become familiar with FDA methods and procedures.

Along with the designated contact, the manufacturer may want operations managers to accompany the investigator, such as the production manager, QA manager, etc. These individuals should be familiar with the plant operations and company policy, and be able to answer questions about procedures and processes. However, a manufacturer should keep the number of individuals accompanying the investigator to a minimum to prevent problems such as contradictory statements.

Receptionists should be informed that FDA investigators will eventually visit and have procedures to follow when they arrive. These procedures should include instructions to call the FDA contact person and what to do or who to contact when that person is not available.

Inspection Refusals

As noted above, Section 704(a) of the FD&C Act gives FDA authority to conduct inspections. Refusing an inspection may set up an adversarial situation and arouse an investigator's suspicion regarding the manufacturer's compliance with the QS regulation. If a manufacturer refuses an inspection without a valid reason, FDA may obtain a warrant which grants entry for an inspection. Refusals to permit inspection are noted in the manufacturer's file maintained by FDA and may be interpreted as a lack of cooperation. Moreover, refusal to permit an inspection is a prohibited act under section 301(f) of the FD&C Act, which may result in sanctions that include criminal prosecution and injunction.

There may be instances, however, when a manufacturer needs to ask the investigator to return at a later time to conduct the inspection. Explain why it is best that an inspection be done at a later time. For instance, if the FDA contact person(s) is not in the factory and no one knowledgeable about the manufacturer's operations is available, it may be appropriate to ask the investigator to come back. However, FDA investigators do expect to be admitted if a device factory is operating. The rationale is that if a factory is operating, someone should be in charge and that individual should

understand factory operations and procedures. If the factory is not in operation or not yet manufacturing any medical devices, this should be explained to the investigator. The FDA representative may still want to go through the factory to make sure it is not in operation -- manufacturers should have a policy covering this situation. It is advisable, in this situation, to allow the investigator to walk through the factory to verify that it is not in operation. If the factory is not in operation, advise the investigator when operations will begin. The investigator will consider the request and circumstances, then determine whether to proceed with the inspection.

Inspection Preliminaries

Before an inspection begins, an investigator is required to show his/her credentials. The credentials have a picture of the investigator and identify him/her as a representative of FDA.

After presenting credentials, the investigator will issue form FDA 482, Notice of Inspection. This form is issued to the owner, operator, or agent in charge of the factory or to the designated FDA contact. The bottom portion of the Notice of Inspection contains excerpts from Section 704 of the FD&C Act. The investigator will complete the top portion of the form by filling in the manufacturer name, address, name of the individual given the signed form, date, and time of inspection. The investigator then signs the form.

The FDA contact person should always be prompt. It is important not to keep the Investigator waiting because misunderstandings can occur regarding the manufacturer's intentions.

Conduct During the Inspection

Awareness of what is going on at all times by the contact person of the manufacturer during the inspection is important. Therefore, once started, the inspection should be given priority. If the contact person is distracted by other business, the inspection may be prolonged and the investigator's questions concerning suspected deficiencies may be misunderstood or answered inadequately. Familiarity with the circumstances surrounding any deficiencies listed on form FDA 483 (the list of deviations presented at the close of the inspection) is vital in discussion of these with the investigator.

During inspections, the FDA contact person will deal with many issues such as viewing records, copying, photos of the manufacturing site, tape recordings, differences of opinion, immediate corrections, promises, samples, notes, etc. All of these issues should be addressed by a company procedure.

There should be a procedure for responding to requests for design history records, device master records, quality system records, device history records, change control records, complaint files, and shipping records. All records required by the QS regulation shall be made available to the investigator for review and copying (820.180). Therefore, records required by the QS regulation shall be readily accessible. The procedures covering review of records by the investigator should identify who will retrieve records, how many records can be reviewed at one time and, who should be present to answer questions raised by the investigator.

Because all records required by the QS regulation shall be available for copying, management should decide on a policy concerning record copying during inspections. In all situations, the contact should make duplicate copies and keep these together as a record of the documents that the investigator copied.

If any records copied by an investigator contain confidential information, they should be identified, i.e., by a confidential stamp. This identification does not automatically prevent release of these records under the Freedom of Information (FOI) Act; however, the FOI officer filling a request is then made aware that the manufacturer considers the information confidential.

Information deemed confidential by the FOI Act or 21 CFR part 20 shall not be released by the agency. Reserve "confidential" marking to only those items that are genuinely confidential..

FDA investigators sometimes photograph equipment, conditions, and product at a facility. FDA feels that picture taking is a normal inspection activity. Include this policy in the inspection procedure.

If the manufacturer disagrees with any observation made by the investigator, be sure to discuss with the investigator the reason for the observation. You may find that there was a misunderstanding that can easily be corrected. When explaining situations or answering questions, be honest. Don't make up answers, as this could lead to additional problems. If you don't know the answer, say so. Personnel with responsibility for representing a manufacturer during an inspection should refer to the FDA regulations and guidances, whenever possible, rather than base discussions and disagreement on personal opinion.

If there are questions for which you don't have immediate answers, promise to research the questions. A list of these unanswered questions is a reminder to get the answers and give them to the investigator. The investigator usually records the questions, and resolving unanswered questions may help avoid inaccuracies on the form FDA 483 and in the establishment inspection report prepared by the investigator at the end of the inspection.

If possible, any GMP deficiencies that the investigator notes, and on which you agree, should be corrected immediately. However, before implementing an immediate corrective action, manufacturers should first evaluate their action to assure that is the best action to take to avoid future quality problems. The investigator should be made aware of these corrections as this will show intent to comply with the regulations and commitment to quality assurance. Corrective actions that are verified by FDA during the inspection will be documented in the investigator's EIR.

If correction cannot be made during the inspection, management may want to consider providing an estimated timetable for correction. However, the manufacturer should not present or commit to a timetable that may be difficult or impossible to meet. If a timetable cannot be immediately developed, try to get one to FDA as soon as possible.

As with any production change, it is a good idea to discuss possible corrective actions with affected company personnel before promising correction to FDA. This concept was discussed in Chapter 8, Device Master Record, and Chapter 9, Document and Change Control, and may prevent promises that have adverse effects on other areas of production. Hastily conceived corrections can cause greater problems in the long run.

Any commitments made to FDA should have top management concurrence. It can be detrimental to the manufacturer to be committed to a course of action that cannot be completed or that management refuses to pursue. Therefore, only persons with the authority to do so should make commitments.

During an inspection, investigators may collect samples. These may be used for a variety of investigational purposes including:

- **to verify conditions in the factory;**
- **to establish interstate movement of finished devices and their components; or,**
- **to fulfill a request from FDA's Center for Devices and Radiological Health (CDRH).**

CDRH may request samples for a number of reasons, such as surveys of device manufacturers and investigation of user complaints. It is a wise policy for a manufacturer to collect and store

duplicate samples whenever an investigator collects samples. If problems are uncovered by FDA, testing of these duplicate samples by the manufacturer may confirm FDA results or form a basis for discussion of FDA findings.

When an FDA investigator collects samples he/she will issue a form FDA 484, Receipt for Samples. Where indicated, interstate movement of the shipments from which these samples were taken will be documented by the investigator with copies of shipping records. The investigator will then prepare an affidavit (forms FDA 463a, 463, 1664a or 1664b) referencing these documents. A responsible employee of the manufacturer will be asked to read the affidavit, identify inaccuracies for correction, and to verify, by signature and/or initials, that the documents referenced in the affidavit pertain to the shipment(s) in question. This action is to formally document interstate receipt or distribution of medical devices. Therefore, the manufacturer should include in its inspection procedure the company policy on the reading and signing of affidavits. Refusal to sign an affidavit is usually noted on the affidavit and in the EIR.

Having accurate and complete knowledge of what an investigator has done is an important part of handling an FDA inspection. Good notes record this information. Comments and suggestions made by the investigator, unanswered questions, and promises should all be recorded. General information on the areas of the plant the investigator visited, to whom he spoke, etc., can help when commenting on form FDA 483 items, making corrections to the facilities or QA system, or advising top management of the results of an inspection.

Notes will also be useful in fulfilling promises or obtaining answers to previously unanswered questions. When the items on the FDA 483 are presented, accurate notes help to prevent surprises. Good notes can also help to prepare well thought out and adequate answers to FDA 483 items even before these items are presented at the close-out meeting.

Close-out Meeting

At the end of an FDA inspection, the investigator conducts a close-out meeting. It is usually held immediately after the inspection, but may take place a day or so later, especially if it takes a long time to prepare form FDA 483. During this meeting, the investigator discusses with company management the observations recorded on form the FDA 483 and other observations not listed that the Investigator wishes to bring to management's attention. The manufacturer should compare the form FDA 483 against notes taken during the inspection to confirm the accuracy and completeness of the investigator's recorded observations. Close-out meetings present an opportunity for all parties to correct such misunderstandings. Inaccurate observations will be changed or deleted as appropriate. Top management should be present at the close-out meeting to provide information regarding any planned corrective actions to be taken and schedules for these actions.

The investigator should be reminded of any corrections that have been made. Corrections that have been made during the inspection will be documented in the investigator's establishment inspection report (EIR) if verified by the investigator if time allows, but these observations will still appear on the FDA 483. Mention your plans to make corrections, and provide a timetable for these future actions. Answers given at this meeting will be recorded by the investigator.

Again, it is important that the company individual promising corrections and setting timetables have the authority to do so. Future inspections will cover those areas where correction was promised as well as other appropriate areas.

After the Inspection

Completion of the inspection by FDA should signal the start of certain activities by the manufacturer, if these activities have not already been initiated, such as discussion of deficiencies

with appropriate department employees to advise them of corrections to be made and time frames involved.

Unresolved form FDA 483 items should be reviewed by company technical and legal personnel. If a decision is made that corrective action is not needed and there is disagreement with the investigator's opinion regarding the deficiency, state this, along with the rationale and documentary evidence, in a letter to the FDA District Office responsible for the inspection. Even if a manufacturer agrees with all the items on the FDA 483, it is a good idea to respond to each item in a letter, along with documentation showing how the corrections have been implemented, to the District Office. The response to the FDA 483 observations should include system corrections and not just "band-aiding" the specific observations. It is very important that the root cause is investigated, where it can be determined, corrected and that appropriate preventive actions take place. This reply shows a commitment to quality assurance and "officially" presents the company's case to FDA. This reply should help resolve any doubts that the inspection report might raise about a manufacturer.

The final step for a manufacturer is to determine what can be learned from the inspection, so that the business can operate in a better state of control, improve quality assurance, and assure future QS compliance.

The following is a concise summary of the major points made in this chapter. This summary should help the manufacturer formulate an inspection plan.

BASIC POINTS FOR AN INSPECTION PLAN

1. **Be prepared for the eventual inspection by trying diligently to comply with applicable medical device regulations and preparing an inspection plan. If needed, assistance is available from DSMA, Phone 800-638-2041 and other offices of the Center for Devices and Radiological Health. Note: DSMA and CDRH can not provide assistance <u>during</u> an FDA inspection by the District office, nor can DSMA provide assistance during an ongoing FDA regulatory action.**

2. **Receptionists should know who to call when an FDA investigator visits.**

3. **Determine that an FDA investigator is calling by examining his/her credentials.**

4. **Receptionists or initial contact persons should inform all key employees that an FDA investigator is present.**

5. **Someone, but not a large number of individuals, should accompany the investigator and be with the investigator at all times.**

6. **If the investigator is not familiar with the manufacturer, describe the product line and operations before entering the manufacturing area.**

7. **At the beginning, review with the investigator all company policies and programs.**

8. **Employees should be cooperative and seek to avoid conflict. Base discussions on the laws, regulations, guidances, etc.**

9. **Don't start an argument with, get up-tight with, or lie to the FDA investigator.**

10. **Understand the investigator's questions before answering. If needed, ask for an explanation. Refer each question to the most suitable employee.**

11. **Be sensitive to the compliance role of the FDA investigator; do not threaten to call his/her supervisor when the investigator is doing his/her job.**

12. **Deviations noted by the investigator should be corrected as soon as possible.**

13. Keep duplicate copies or samples of material given to the FDA investigator.

14. During the exit interview, make sure that all deviations are adequately discussed. If there is disagreement, present all of the company information and any regulations and official interpretations that support the company's viewpoint.

15. Immediately submit to the local FDA District office a written reply to the FDA 483. Make sure you address all of the observations. State how and when you expect to make corrections. If you disagree with an observation, give reasons and references to regulations, guidances, etc., for your position.

16. Be reasonable in setting schedules for corrective actions -- don't state impossible deadlines or drag out completion schedules.

17. A follow-up report covering findings and corrections should be distributed to appropriate company employees.

REGULATORY SANCTIONS

Responsible officials, who are in positions of authority at regulated manufacturing sites, have a primary legal duty to implement whatever measures are necessary to ensure that their products, facilities, and operations are in compliance with the law. The law presumes these individuals are fully aware of their responsibilities.

Whenever FDA determines, as a result of an inspection, investigation, complaint, or other source, that a product is, or may become, adulterated or misbranded, several actions may be taken. These actions may be in the form of a warning letter to the manufacturer; or result in the seizure or detention of a product; or an injunction of the firm and/or responsible individuals; or result in prosecution of the manufacturer and/or responsible individuals. The actions vary depending on the degree of danger to the public or willingness of the manufacturer to correct violations. [Following are several sections of the Food, Drug, and Cosmetic (FD&C) Act commonly used in misbranding or adulteration charges. In this reprint, some key words are bolded for emphasis. Added notes are in brackets.]

Adulteration

Section 501 (351). A drug or device shall be deemed to be adulterated --
(a)(1) If it consists in whole or in part of any filthy, putrid, or decomposed substance; or

(2)(A) If it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health;

(c) If it is not subject to the provisions of paragraph 9(b) of this section* and its strength differs from, or its purity or quality falls below, that which it purports or is represented to possess.

[* Paragraph 9(b) refers to drugs].

(h) If it is a device and the methods used in, or the facilities or controls used for its manufacture, packing, storage, or installation are not in conformity with applicable requirements under Section 520(f)(l) or an applicable condition prescribed by an order under Section 520(f)(2).

Misbranding

Section 502 (352). A drug or device shall be deemed to be misbranded --

(a)If its labeling is false or misleading in any particular.

If in a package form unless it bears a label containing (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count ...

(f) Unless its labeling bears (1) adequate direction for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods of duration of administration or application, in such manner and form, as are necessary for the protection of users ...

(j) If it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof.

A device may be considered misbranded for other administrative reasons such as failure of the manufacturer to register, formally list the product, or failure to submit a premarket notification (21 CFR Part 807).

When it is consistent with the public interest, it is FDA's policy to: advise regulated manufacturers of potentially violative products, practices, or conditions; advise manufacturers of violations requiring correction; and, give manufacturers an opportunity to make corrections voluntarily before initiating legal or administrative action.

Management Letter

When top management is not present during the issuance of the FDA 483 at the end of the inspection,
FDA may send a Management Letter to top management such as the president, CEO, etc., to assure that top management has a copy of the FDA 483. Because the Management Letter is only a brief transmittal letter, it is not to be considered or confused with the Warning Letter described below.

It is imperative that the manufacturer respond to any recommendations or observations made by the FDA investigator or other official. A written response to the FDA 483, along with documentation to show how the manufacturer has or intends to remove or correct the objectionable conditions or practices, can assure the FDA that the manufacturer has corrected or intends to correct listed violations. The manufacturer should prepare such a response even if they do not hear from FDA in writing. To repeat, a plan of corrective action is very important. Management should evaluate the FDA 483 and their management letter. If they feel any misunderstanding can be resolved by discussion, they may also request a meeting with district management to discuss violations and the manufacturer's proposed courses of action. This approach gives a first hand opportunity to present the case to FDA.

Warning Letter

A Warning Letter is a specifically worded and formatted enforcement letter written by top management of an FDA field or headquarters unit to top management of a manufacturer. The letter is sent by FDA primarily to draw the company's attention to violations and, thereby, obtain prompt correction. A Warning Letter is intended to effect correction of deficiencies noted: during an inspection; from an investigation of a product complaint; or from information received from other sources. A purged Warning Letter is reprinted at the end of this chapter.

A Warning Letter may be issued by FDA instead of immediately seizing product or obtaining an injunction against the manufacturer. The Warning Letter contains a formal warning to the

manufacturer advising that specific sections of the law have been violated and, unless corrective action is taken, the FDA is prepared to impose legal and/or administrative sanctions. Sanctions include seizure, prosecution, injunction, and civil penalties. Unless otherwise indicated, within 15 working days after receiving a Warning Letter, a formal response should be made by the manufacturer to FDA. The manufacturer should state the specific steps it has taken to correct noted violations, including an explanation of each step taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

A Warning Letter is also a prior warning and notification to responsible company officials of possible civil or criminal action to be taken by FDA.

Responsible individuals should not assume they will always receive a Warning Letter before FDA initiates administrative action or recommends an injunction, seizure, civil penalty, and/or criminal proceeding. FDA is under no legal obligation to warn manufacturers or individuals that they or their products are in violation of the law, before initiating formal regulatory action.

Remember, the issuance of a Warning Letter to the manufacturer by FDA does not preclude the initiation of other concurrent action, such as seizure, as part of an overall enforcement strategy.

Seizure

A seizure is a civil court action against a specific quantity of goods whereby FDA seeks to remove these goods from commercial channels. After seizure, no one may tamper with the seized goods except by permission of the court. The claimant of the seized merchandise may file a claim and an answer, or may take no action. If no action is taken,the government will move to have the goods forfeited to the government by default. If a claimant decides to contest the Government's charges, the case will be scheduled for trial. A third option allows the owner of the goods to request permission of the court to bring the goods into compliance with the law. The owner of the goods is required to provide a bond (money deposit) to assure that the orders of the Court will be performed and the owner will be ordered to pay for FDA supervision of any activities by the company to bring the goods into compliance.

Detention

An administrative detention prohibits the distribution or use of adulterated or misbranded devices encountered during inspections. The detention usually lasts up to 30 days, and can last longer, until FDA has considered what action it should take concerning the devices, or has initiated legal action if appropriate. During the detention, detained devices may not be used, moved, altered, or tampered with in any manner by any person.

Restraining Orders and Injunctions

A Temporary Restraining Order (TRO) is sought by FDA before an injunction and is designed to stop the alleged violative practice until the court can hear evidence that may lead to an injunction. A TRO imposes restraint upon a defendant for not more than 10 days; this period may be extended by the courts.

An injunction is a court order that restrains a person or manufacturer from violating the law, e.g., to prevent interstate distribution of violative products, and to correct conditions in the establishment in which the violation occurred. FDA may also seek a preliminary injunction. To obtain this preliminary form of relief, the government needs only to show that the law has been violated, and that it will probably continue to be violated unless the court enjoins the violative behavior.

Recalls

The Food and Drug Administration prefers to promote compliance by means other than through the courts. Recall by the manufacturer of violative products from the market is generally the fastest and most effective way to protect the public. A recall may be initiated by the manufacturer or shipper of the product, or initiated by FDA. The first step in a product recall is for the manufacturer or distributor to contact the nearest FDA field office for guidance. FDA can provide technical assistance to small and large manufacturers on how to conduct an effective recall.

It is recommended that manufacturers develop plans which can be put into effect immediately if a recall emergency arises. Accurate and complete product and shipping records are vital to the success of a product recall. Products should be labeled (direct or by code) to show date and place of manufacture.

Recently, FDA has observed that when a manufacturer discovers a risk presented by a medical device, it often voluntarily notifies appropriate persons of this risk in order to reduce or eliminate it. In some cases these notifications meet the definition of recall in 21 CFR Part 7.3(g). There is a proposed rule 21 CFR 810 issued on June 14, 1994, that would establish procedures to implement the medical device recall authority provided in the SMDA. This authority will add to other remedies already available to FDA including rectification, repair, replacement, and refund.

Because of concern that a notification might be classified as a recall, manufacturers have sometimes delayed issuing a notification while discussions are held with FDA. To try to eliminate delays in situations where public health might be at risk, FDA published, "Medical Device Notification and Voluntary Safety Alert Guideline," in March 1984, which contains procedures that manufacturers should use in notifying or alerting health professionals who prescribe or use a medical device. These procedures also describe the steps used by FDA in the notification and safety alert process.

Penalties

FDA has authority to impose civil penalties. Manufacturers are liable for a maximum of $15,000 per violation of the FD&C Act, with a cap of $1,000,000 per proceeding. See Section 303 of the FD&C Act for details of additional penalties. Also, see the Safe Medical Devices Act of 1990 for more details on FDA's authority to impose penalties.

EXHIBITS

Associated with inspections are various FDA forms. Examples of forms are included at the end of this chapter. The form (FDA) numbers are in the lower left corner of each sheet.

Notice of Inspection

The first form is the FDA 482 (Notice of Inspection) which is issued at the beginning of the inspection. It includes blanks for basic information on the manufacturer, the investigator's name, and contains a reprint of applicable sections of the FD&C Act and Public Health Service Act. This form is to be signed by the investigator and given to the individual noted on the form.

Receipt for Samples (page 18-14)

If an investigator collects samples, form FDA 484 (Receipt for Samples) is issued to the company agent. A copy of the receipt needs to be submitted with the firm's invoice or other billing documents if payment has beed agreed to by the firm and the FDA Investigator. This form contains the name of the individual given the form, manufacturer information, and sample description. The investigator signs the form and issues it to the individual noted on the form.

Affidavits (pages 18-15 to 18-18)

The next four forms are used where interstate movement of devices is documented by collection of shipping records. The investigator prepares an affidavit (forms FDA 463a, 1664a, or 1664b) referencing these shipping records. A brief statement is included along with space for a description of the documents that relate to the interstate movement of the sample in question. Each form is signed by the investigator and the person giving the information. On one of the sample forms, FDA 463a, the individual giving the information refused to sign the affidavit; and in this case the investigator added a statement to explain the lack of a signature.

List of Observations (page 18-19)

During an inspection, an investigator will note what is considered to be GMP deviations, or deviations from a manufacturer's established procedures. These observations comprise the form FDA 483 (List of Observations) which is issued to the company. The observations are listed in the large blank area of the form, and the form is signed by the investigator. (Page 18-19)

Establishment Inspection Report (pages 18-20 to 18-34)

The final example is the "Establishment Inspection Report". After completion of an inspection, an investigator prepares a comprehensive EIR covering a manufacturer's operations, items on the FDA 483, plus the details that support the FDA 483, and any corrective actions taken by the manufacturer. A manufacturer may receive an unpurged copy of their EIR report under the Freedom of Information (FOI) Act by requesting it in writing from their local FDA District Office. Copies of EIR's requested through FOI by other than the inspected manufacturer will be purged of confidential or trade secret information. The fictitious sample EIR near the end of this chapter has certain lines highlighted to simulate purging. The normally purged material is left in the simulated EIR to show the type of information that would be purged.

Warning Letter (pages 18-35 & 18-36)

AFFIDAVIT

SAMPLE NO. 82-876-543

STATE OF Oregon COUNTY OF Klamath

Before me, Sidney H Rogers, an employee of the Department of Health and Human Services, Food and Drug Administration, designated by the Secretary, under authority of the Act of January 31, 1925, 43 Statutes at Large 803, Reorganization Plan No. V, Sec. 2(15), effective June 30, 1940; Reorganization Plan No. 1 of 1953, Secs. 1-9, effective April 11, 1953, and P.L. 88-88, Sec. 509, 77 Statutes at Large 165 (20 U.S.C. 3508), effective May 4, 1980, to administer oaths, affirmations, and affidavits, personally appeared George F. Thompson, a resident of the county and State aforesaid, who, being duly sworn, deposes and says:

I live at 2209 Timberline Ave., Klamath Falls, Oregon In Response To An Ad in the August, 1982 "Cascade Sun" I ordered From Los Gatos Associates, 920 Apricot St., San Jose, California, 4 Energizer Devices for use in my practice.

On 8-20-82 Mr. George Hughes, Abricio Ave., Klamath Falls, Oregon, delivered To my office the Four devices All labeled in part "Isotope Enerjizor ™ Model MARK I ™ Distributed by Los Gatos Associates, San Jose, Calif." Serial numbers 2904, 2905, 2906, and 2907. Mr. Hughes picked up these devices in San Jose for me as he makes Regular Trips There in his pickup truck to buy Fruit.

On 9-2-82, U.S. Foods Drug employee, Sidney H. Rogers Took photographs of the devices and copied the labeling of the Four Enerjizor devices in my office located at 2209 Timberline Ave., Klamath Falls, Oregon

9-2-82
George F. Thompson, D.C.
Read this Affidavit and
Avowed it to be true but
declined To sign it
Sidney H Rogers

George F. Thompson

AFFIANT'S SIGNATURE AND TITLE

George F Thompson, D.C.

AFFIANT'S NAME AND ADDRESS (Include ZIP Code)

Subscribed and sworn to before me at _____ (City and State)

this ___ day of _____, 19 ___.

_____ (Employee's Signature)

Employee of the Department of Health and Human Services designated under Act of January 31, 1925, Reorganization Plan IV effective June 30, 1940; Reorganization Plan No. 1 of 1953 effective April 11, 1953, and P.L. 96-88 effective May 4, 1980.

FORM FDA 4003 (4-83) PREVIOUS EDITIONS MAY BE USED. PAGE ___ OF ___ PAGES

AFFIDAVIT (Jobber)

Sample No. 83-135-791

STATE OF PENNSYLVANIA COUNTY OF Philadelphia

Before me, SIDNEY H. Rogers, an employee of the Department of Health and Human Services, Food and Drug Administration, designated by the Secretary, under authority of the Act of January 31, 1925, 43 Statutes at Large 803; Reorganization Plan No. IV Sec. 19-15, effective June 30, 1940, Reorganization Plan No. 1 of 1953, Sec. 1-9, effective April 11, 1953; and P.L. 96-88, Sec. 509, 93 Statutes at Large 965 (20 U.S.C. 3508), effective May 4, 1980, to administer or take oaths, affirmations, and affidavits, personally appeared PATRICK T. Palmer in the county and State aforesaid, who, being duly sworn, deposes and says: the Lot of 325 CASES, (24/4½oz CANS) OF Jolly MILLER CANNED MUSHROOMS

which we invoiced and sold to PATRIOT MARKETS, INC, FRANKFORD PENNSYLVANIA on 4-12-83

was a portion/all of a parcel shipped to us by NORTHERN Light Foods, INC. Duluth, MINNESOTA

and is covered by submitted (copy of) invoice(s):

	NUMBER	DATE	NUMBER	DATE	NUMBER	DATE
1)	3914	4-4-83	2)		3)	

and (copy of) shipping record(s):

	TYPE (B/L, F/B)	NUMBER	DATE	ISSUING FIRM OR CARRIER
1)	B/L	20018	4-5-83	NORTHERN FREIGHT CARRIERS
2)	—			
3)	—			

REMARKS

APPLICANT'S SIGNATURE AND TITLE Patrick T. Palmer - Warehouse Manager

FIRM (Name and address, include ZIP Code) LIBERTY WHOLESALE GROCERS, 3210 M AVE, FRANKFORD, PA. 19105

Subscribed and sworn to before me at FRANKFORD, PA. (City and State)

this 28th day of APRIL 19 83

Sidney H. Rogers (Employee's Signature)

Employee of the Department of Health and Human Services designated under Act of January 31, 1925, Reorganization Plan IV effective June 30, 1940; Reorganization Plan No. 1 of 1953, effective April 11, 1953; and P.L. 96-88, effective May 4, 1980.

FORM FDA 1864a (4/83) PREVIOUS EDITIONS ARE OBSOLETE

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER Minneapolis District 240 Hennepin Ave. Minneapolis, MN 55401 (612) 725-2121
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: William S. Gundstrom	DATE OF INSPECTION Jan. 5 thru 7,1982
TITLE OF INDIVIDUAL Vice President - Production	TYPE ESTABLISHMENT INSPECTED Table: Repacker
FIRM NAME Topline Pharmaceuticals "T.L.P."	NAME OF FIRM, BRANCH OR UNIT INSPECTED "T.L.P." Division 03
STREET ADDRESS 2136 Elbe Place	STREET ADDRESS OF PREMISES INSPECTED 80 Elbe Court
CITY AND STATE Jackston, MN 55326	CITY AND STATE N. Jackson, MN 55320

DURING AN INSPECTION OF YOUR FIRM (I) ~~visit~~ OBSERVED:

List your observations in a logical and concise manner.

(See IOM 512, 512.1, & 512.2)

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Sidney H. Rogers	EMPLOYEE(S) NAME AND TITLE (Print or Type) Sidney H. Rogers Investigator

FORM FDA 463 (8/82) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE 1 OF 1 PAGES

ESTABLISHMENT REPORT (EIR) PURGED

SUMMARY OF FINDINGS

This inspection was conducted in accordance with the NYK-DO June 1986 Workplan, under CP 7378.830 Inspection of Medical Device Manufacturers, and under CP 7378.830A Sterilization of Medical Devices. This inspections was also conducted to follow up medical device complaint M-00210, dated 5/31/84, re: leaking of a Cardio-Minipor IV Filter (no specific lot number).

This firm produces various sterile disposable blood filters and cardiovascular catheters. This inspection was limited to the firm's sterile blood filter which is intended for extracorporeal use as indicated during any cardiopulmonary bypass procedure (open heart surgery). This product is currently classified as a noncritical device.

Previous inspection 6/82 was performed as a follow up to PHI-DO memo 4/2/82 (J.L. Smith) requesting information on validation studies, and the firm's controls for testing for sterility and ~~ETO~~ residues. PHI-DO's inspection of a contract sterilizer, ~~Minix Lab, Erie, PA~~, revealed the firm had no validation study and that the firm failed to follow its own established ~~ETO~~ process parameters. NYK-DO's 6/82 inspection revealed that sterility testing and controls were adequate, that an ~~ETO~~ residue study had been conducted and that the firm was conducting a validation study. No FD 483 was issued, and no samples were collected.

Next previous inspection, 12/20/81, was conducted as a follow up of two medical device problem reports, M32012 and M32190, both concerning leakage during use of the firm's IV filter. Inspection revealed that the product probably failed due to its being used as pressures in excess of 600 mm Hg, as filters from the same lot passed this specification upon retesting. No FD 483 was issued.

The current inspection revealed some deficiencies in the firm's master device record for the blood filters. No other deficiencies were noted. The deficiencies were listed on an FD 483, which was presented to and discussed with management at the close of the inspection. Deficiencies noted in the master device record are:

1. **it does not list acceptance criteria for incoming components;**

2. **it does not list that components made of plastic are to receive an IR spectrographic analysis;**

3. **it does not list that the ~~cellulose acetate~~ filtering material is about ~~120~~ mesh, nor does it list the quantity of this material that is used to manufacturer blood filters;**

4. **the operation sheets have not been signed by all approving officials;**

5. **the engineering diagrams for the housing, and top end cap do not bear the signature/initials of an approving corporate official.**

Management promised correction of the noted deficiencies, and stated that they had already attended to the first point (Ex. 8). No samples were collected during this inspection.

Investigation of complaint M-00210 revealed that the IV filter had probably been subjected to pressures in excess of 600 mm mercury. The product is labeled for use below 600 mm mercury.

Current inspection also revealed that the firm intends to discontinue using ~~Minix Lab~~ as the contract sterilizer. The firm intends to develop/perform its own ~~ETO~~ sterilization procedures within the next year.

On 6/7 to 9/84, I was accompanied by John Goodguy. Mr. Goodguy represents the Center for Devices and Radiological Health, Division of Small Manufacturers Assistance. Mr. Goodguy wanted to become familiar with the way FDA field offices were conducting medical device inspections. Mr. Goodguy's tight schedule did not permit him to accompany me for the complete inspection.

HISTORY OF BUSINESS

The firm is a New York State corporation with the following corporate officers:

Mrs. Alice B. Potts	**-**	**Chairman of the Board**
Mr. John (NMI) Fogg	**-**	**President**
Mr. William L. Pearl	**-**	**Senior Vice President**
Mr. Walter Y. Ratkowski	**-**	**Vice President and General Manager**

Cardio-Medical Products, Inc. is a wholly owned subsidiary of Medical Products USA, Inc. and both firms occupy the same premises. The corporate officers of Medical Products USA, Inc. are:

Dr. Michael P. Heart	**-**	**Chairman of the Board**
Mrs. Alice B. Potts	**-**	**President**
Dr. Mary L. Day	**-**	**Executive Vice President**
Mr. John (NMI) Fogg	**-**	**Senior Vice President**

Filters are manufacturers under the Cardio Minipor trade name and in general are intended for hospital use. The firm manufacturers four types of filters, as follows:

1. **Blood Dialysis Filters**
2. **Cardiopulmonary Bypass Blood Filters**
3. **Infusion Line Filter**
4. **IV Filter**

The firm operates 3 shifts (24 hours per day) Mon.-Fri., except for two weeks around Christmas. The firm also closes for two weeks in July for major cleaning operations. The firm is currently registered as a medical device establishment.

PERSONS INTERVIEWED AND INDIVIDUAL RESPONSIBILITY

At the start of the inspection credentials were shown and an FD 482, Notice of Inspection, was issued to Mr. John (NMI) Fogg, President. Credentials were also shown to Dr. Paul M. Turner, Ph.D., Quality Assurance manager, and to Mr. Thomas (NMI) Romano, Quality Control Manager.

During this inspection, I was also introduced to: William L. Pearl, Senior Vice President; Walter Y. Ratkowski, Vice President and General Manager; Charles Miller, Asst. QC Manager; Alice Oprice, QA Technical Assistance; Joseph DiRisio, Metrologist; Harold Miller, Operations Manager; and Katherine Anderson, Materials Manager. Mr. Fogg and/or Dr. Turner accompanied me during most of the inspection and supplied most of the relevant information. Some relevant information was also supplied by the above named individuals.

At the close of the inspection and FD 483, Inspectional Observations, was issued to and discussed with Mr. Jonn (NMI) Fogg, President.

Key officers/plant personnel are as follows:

John (NMI) Fogg	**-**	**President**
William L. Pearl	**-**	**Senior Vice President**
Walter Y. Ratkowski	**-**	**Vice President and General Manager**
Dr. Paul M. Turner	**-**	**Quality Assurance Manager**
Thomas (NMI) Romano	**-**	**Quality Control Manager**
Charles Miller	**-**	**Asst. Quality Control Manager**
Harold Miller (brother)	**-**	**Operations Manager**
Joseph DiRisio	**-**	**Metrologist**
John Dace	**-**	**Vice President**

Mr. John Fogg stated he was the firm's president and chief executive officer, and bore overall responsibility and authority for the firm's activities (see Ex. 1, pg. 4). Mr. Fogg stated that he could authorize capital expenditures on his own authority, and that he did not have to obtain authorization from any official of the parent firm before making a capital expenditure. Mr. Fogg stated he was responsible for authorizing research and development programs, marketing programs, allocation of space, new construction, plant maintenance, acquisition of capital equipment, labeling changes, and for authorizing any studies such as validation studies, bioburden studies, and residue studies.

Mr. Fogg stated that William L. Pearl, Sr. VP, was responsible to him for engineering; that Dr. Paul M. Turner, QA Manager, was responsible to him for the QA program; that Thomas Romano, QC Manager, was responsible to him for the routine review and approval of device history records and for the release of lots from quarantine; that Harold Miller, Operations Manager, was responsible to him for production and warehouse activities; and that Walter Ratkowski, VP and General Manager, was responsible to him for sales and marketing operations. Mr. Fogg stated he has a BS in Chemistry from ~~Furman University, Greenwich, South Carolina~~, has been with the firm since 1962, and has been president for about the last eight years.

During the inspection Mr. Fogg directed various employees, such as Dr. Turner, Mr. Romano, Mr. Harold Miller, and Ms. Oprice to provide me with requested information. These requests for information were honored by the various employees.

William L. Pearl, Sr. VP, stated he was responsible to John Fogg for engineering. These responsibilities include reviewing and approving engineering diagrams, research and development projects for new equipment and new products, and performing major equipment overhauls. Mr. Pearl has been with the firm since 1969 and has a BS in Mechanical Engineering from ~~Duke University, Durham, North Carolina~~.

Walter Y. Ratkowski, VP and General manager, is responsible for sales and marketing operations to John Fogg. As a follow up to a product occurrence report (complain) Mr. Ratkowski is responsible for determining if and when complimentary replacement units are to be sent out. Mr. Ratkowski has a BS in Chemical Engineering from the ~~University of Toronto~~ and has been with the firm since 1968.

Paul M. Turner, QA manager, stated he was responsible to John Fogg for the quality assurance program of Cardio-Medical Products, Inc. These responsibilities include the periodic auditing of production, lab quality control, and metrology procedures, implementing studies authorized by Mr. Fogg, and ensuring that the firm meets its regulatory responsibilities and complies with GMP regulations. Dr. Turner stated that it was his responsibility to prepare and submit 510(k)s to the FDA. Dr. Turner has his Ph.D. in Chemistry from ~~Western Michigan University, Kalamazoo, Michigan~~ and has been with the firm since 1976.

Thomas Romano, QC Manager, stated he is responsible to Mr. Fogg for renewing and approving device history records to determine if a lot of finished filters can be released from quarantine and entered into inventory, for the inspection and approval of incoming components, for the activities and records of the QC labs in performing tests on incoming components, in process products, environmental plates, bioburden, and pyrogen.

Mr. Romano stated he coordinates complaint investigations by reviewing complaints and deciding which department(s) will be responsible for investigating the complaint, and is responsible for sending out responses to complaints when necessary. Mr. Romano stated that Mr. Charles Miller, Asst. QC Manager, assists him in his duties. Mr. Miller is also responsible for maintaining the firm's reserve samples, which are used for stability study purposes only. Mr. Romano has his BS in Chemistry from ~~Wright State, Dayton, Ohio~~ and has been with the firm since 1978. Mr. Charles Miller has his BS in Biology from ~~Yale University, New Haven, Connecticut~~ and has been with the firm since 1977.

Joseph DiRisio, QA Metrologist, stated he was responsible to Dr. Turner for all of the firm's metrology (measurement and calibration) functions, and that he originated the firm's metrology manual (Ex. 4). Mr. DiRisio stated he was formerly the metrologist for ~~American Armature Co., Cleveland Ohio~~ and that he has been with the firm since 1976.

Harold Miller, Operations Manager, stated he was responsible to John Fogg for production and warehouse operations. Mr. Miller is also responsible for ordering raw materials and for routine maintenance and clean up operations. Mr. Miller has his BS in Mathematics from ~~New York University~~ and has his MS in Industrial Engineering from ~~Columbia University, New York, New York~~ and has been with the firm since 1979.

GUARANTEES AND LABELING AGREEMENTS

The firm does not offer and FD&C guarantees. Dr. Turner stated that the firm does have agreements with some of their component suppliers whereby suppliers have agreed to notify Cardio-Medical of any changes in components. testing or procedures related to the manufacture of the components. Dr. Turner provided me with copies of these agreements (Ex. 10). These agreements appear to satisfy the GMP regulation re: critical component supplier agreements, although the firm is not required to have these agreements as the device is currently classified as a non-critical device. The firm also ships some filters in bulk to overseas divisions/subsidiaries of Cardio-Medical Products, Inc. without the need of a labeling agreement.

FIRM'S TRAINING PROGRAM

The firm's training program for production employees consists of on-the-job training and lectures. Mr. Fogg stated that any formal training given to employees is documented and recorded in the employee's personnel file. I requested Mr. Fogg to remove the documentation of Mr. Joseph DiRisio's training from hsi personnel file for my review. Training was adequately documented.

RAW MATERIALS

Raw materials and components used to manufacture the firm's blood filters include:

Materials		Suppliers
~~Gellulose Acetate~~	-	~~Macomb Laboratories, inc. (Bohemia, NY)~~
~~Bonding epoxy~~	-	~~Ideal Materials Co. (Toledo, Ohio)~~
~~Polyprepylene end cape~~	-	~~ABO Excruders Inc. (Los Angeles, CA)~~
~~Glycerine Lubricant~~	-	~~Sigma Laboratories (Miami, Florida)~~
~~Ultrasonic cleaning solution~~	-	~~Ace Science Inc. (Kenilworth, NJ)~~
~~Polypropylene tubing~~	-	~~ABO Excruders Inc. (Los Angeles, CA)~~

Components used to manufacture the firm's filters are listed in Ex. 6 Suppliers' addresses are listed in Ex. 7.

Components are stored in the firm's warehouse, located down the block at 2700 Ogden Street. Incoming components are stored in a chaged quarantine area in the warehouse. When components are inspected and found to be acceptable, cartons containing the components are each ink stamped "ACCEPTED." The firm does not use the system of designating quarantined components with a "QUARANTINE" stamp of sticker, and then subsequently identifying the component as "ACCEPTED" or "REJECTED."

Mr. Fogg stated that Quality Control inspectors inspect incoming components for characteristics as specified in the master device record. Ex. 8 is an example of the characteristics for some of the blood filter components listed in the master record. Though QC inspects components for these characteristics, no pass-fail specifications were noted during the inspection. This was pointed out to Mr. Fogg and Dr. Turner. By the conclusion of the inspection, Mr. Romano had drafted up such a specification, as is shown on Page 1 of Ex. 8.

All incoming components are assigned a control number, which reflects the purchase order number (P.O.#). For example, if P.O.#23466 is for 200 cartons of filtermesh and the order is

received from the supplier in several shipments, then the cartons in the first shipment will be identified with control number 23466-1, and the cartons in the second shipment will be identified 23466-2, and so on until all the cartons shipped under this purchase order are received. This information is recorded manually as well as fed into the firm's computer. The computer is used for inventory control and facilitates the firm's first-in, first-out policy.

Mr. Romano described the components inspection procedure. Components are inspected for the characteristics specified in the deice master record (see Ex. 8) which requires that 10% of the log, up to 1,000 units, be inspected. A QC inspector can accept the lot if he finds no defective units; otherwise a deficient lot will have to be approved by the firm's Materials Review Board (William Pearl, John Fogg, and Thomas Romano).

During the inspection a QC Inspector was noted to be inspecting an incoming lot of housing units for the blood filter. Upon questioning, the inspector stated that he checks the housing units using a ~~B&L 200X stereoscopic microscope~~ and standardized ~~micrometer~~. The inspector stated he ~~checked each sampled unit for burro and sharp edges using the microscope. The micrometer was used to check the wall thickness of the housing. The tolerance spec for the wall thickness was 0.01 cm.~~

Using one of several microscopes, the firm's QC lab checks the ~~cellulose acetate~~ filtering material for mesh count of every lot of mesh received, and records the results of the inspection in a log book. This log book cross-references the purchase order number of the lot.

OPERATIONS

The firm occupies a two story building in a light industrial area: the first floor is mainly for plant operations and the second floor is mainly for office space. As previously stated, the premises are shared between Cardio-Medical Products, Inc. and Medical Products USA. Cardio-Medical Products has 65 employees, working three shifts Mon.-Fri. The firm is closed for two weeks around Christmas and In July. The firm has a warehouse at 2700 Ogden Street which is used to store raw materials and finished products. Finished products ready for ETO sterilization are shipped to the contract sterilizer via company trucks. Finished products ready for distribution to consignees are usually shipped via ~~UPS~~.

Mr. Fogg estimated that his firm manufactured about ~~10,000~~ blood filters last year, of which about ~~3,000~~ were used for arterial use, and about ~~7,000~~ were used for cardionomy use. Blood filters are manufactured to be compatible with either ½ inch or 1 inch connectors. The bulk of the firm's blood filters are manufactured with ½ inch connectors.

The manufacturing operations are listed and described in the master device record's "OPERATION SHEETS." Ex. 11 is an example of some of the "OPERATION SHEETS." In essence, the manufacturing process consists of the following operations:

1. **~~Molding of plastic parts. Appropriate quantities of virgin resin (60%) and regrind resin (20%) are selected and weighed. Red #12 is added and the material is mixed~~.**

2. **~~The above mixture is dated and given a lot number and placed into a sized tumbling device (Rich Hopper) for blending for 6 hours~~.**

3. **~~Prior to using the molding, machine is purged of any previous materials. A mixture of mold release agents is used. This is forced thru the system using air at 50 PSI~~.**

4. **~~After flushing with mold release agents, the system is lubricated using a glycerin lubricant manufactured by Sigma Labs, Miami, Florida~~.**

5. **~~The molding machine is set up using the appropriate mold. The firm has 4 different molds. Two molds are used for the arterial filter, one for 1 inch connectors and one for ½ inch connectors. The other 2 are for cardionomy filters, again 1 for 1 inch and the other for ½ for ½ inch connectors~~.**

6. **~~When the plastic parts have been molded, the cellulose acetate filtering material must be inserted. This is done by a special machine which places one layer of material on top of another. The completed filter has a total of 60 layers for the arterial model and 75 for the cardionomy model~~.**

7. **~~After the cellulose acetate has been inserted into the filter, the end cap is placed on the open end and bonded using a bonding epoxy. This operation is performed using a specially designed capping machine. Epoxy is applied to the cap at one state of the machine operation, then the cap is inserted into the body of the filter. The machine then twists the cap into place~~.**

8. **~~Once the cap and body have been applied, the polyurethane tubing is attached to either end of the filter. The tubing is received in a large spool and cut to the proper length using a Ronfro tube cutter model 54~~.**

9. **~~The finished filter is then placed into its metal housing and then into polypropalene bags which are sealed using a Smith #2 heat sealing machine. The bags are then loaded into cartons, 10 filters to a carton for shipment to the contract sterilizer. Each carton is labeled as "caution, this product has not yet undergone sterilization"~~.**

10. ~~When the sterilized product is returned, samples are removed and the cartons placed in a quarantine area. When the results of the sterility test are received, the cartons are marked "approved for packaging." The final step in the process is the packaging of the filters into labeled cardboard unit packages. This is accomplished using a Packo Packaging machine model #8245. Once packaged, the product is stored in a quarantined area until released for shipping~~.

Samples designated for testing are pulled by QC. The firm performs its own ~~Bubble Point SSP/NF~~ testing of each lot of filters prior to ~~ETO~~ sterilization. See Ex. 16 for ~~USP/NF Bubble Point~~ testing procedures and Ex. 17, pages 20-22, for some ~~Bubble Point~~ log book records. See Ex. 14 for bioburden testing procedures and Ex. 17, pages 23 and 24, for ~~LAL Pyrogen Testing~~ log book records.

Filters designated for sterility testing are held separate from the rest of the lot until the lot is ready for shipment to the contract sterilizer. Samples designated for pyrogen and safety (toxicity) testing, by outside labs, area also pulled at this time.

The firm's QC lab was noted to have on hand the ~~Jones Bubble Point Testing Apparatus~~ to test the filters prior to ~~ETO~~ sterilization. These were ~~calibrated at 0.001 ml. of air per cubic inch~~.

The firm also performs its own ~~LAL~~ pyrogen testing. This pyrogen testing is performed on the IV filter only, as only these filters have a ~~Lewis Crenshaw~~ filtering media. All other filters have ~~Wren~~ media, which are not as likely to support bacterial growth as ~~Lewis Crenshaw~~ media. The firm's QC lab had ~~Pyro Gen Lab test serum and testing apparatus~~. Review of ~~LAL~~ testing records going back 6 months revealed no positive results. Charles Miller, Asst. QC Manager, stated that QC lab uses a ~~40% alcohol solution as first a rinse on the filter, a 25% solution as a second rinse to collect the solution used for pyrogen testing and a 10 unit sample for each testing run~~.

The rest of the cartons in the lot are pelletized and the pallets are completely wrapped with large sheets of cardboard and banded with steel bands to discourage tampering. Each pallet is identified with a Cardio-Medical sterilization lot number, which is a number that can be correlated to the contract sterilizer's sterilization lot number. Each pallet is also identified with a contents statement, indicating the product numbers, day lot numbers, and the number of cartons of each lot contained on the pallet. A Cardio-Medical truck will take up to 6 pallets of products to the contract sterilizer, ~~Minix Lab, Brie, PA about once a week~~. The filters designated for testing by outside labs are shipped along with the pallets to the contract sterilizer. Through contractual agreements Cardio-Medical has notified the contract sterilizer of the desired placement of the test samples within the sterilizer, as shown in Ex. 20, Pg. 3. For each sterilization lot Cardio-Medical notifies the contract sterilizer which samples are not to be sent to which outside labs. A Cardio-Medical truck will pick up he lot after it has been sterilized, and return it to the Cardio-Medical warehouse at 2700 Ogden Street, where the lot is placed in quarantine until the test results are returned and approved.

In the meantime, QC personnel will open up ~~6~~ cartons from each day lot of all the day lots in each sterilization lot and inspect the plastic bags for any air leaks/burst bags. If any air leaks/burst bags are found, then every carton in the day lot is opened to determine how extensive the problem is. Leaks/burst bags indicate either the bags were not sealed properly and/or that the contract sterilizer pulled a vacuum larger than they should have during the ~~ETO~~ sterilization cycle. Lots found with the significant numbers of leaks/burst bags are ~~re-bagged and subjected again to ETO~~.

Once the QC Manager approves of the QC inspection tests and approves of the outside testing lab results (sterility, pyrogen, and safety), then he will sign the lot release report (Ex. 17, Pg. 1) which permits the release of the lot from quarantine and entry into inventory.

Mr. Charles Miller stated that he maintains the firm's reserve samples which are collected 10 times a year and are used for shelf life studies (see Ex. 22). No other reserve samples are taken. Shelf life studies testing includes tests for ~~Bubble Point, Porosity and Sterility~~.

Regarding components and products rejected during processing, Mr. Fogg stated that all rejects are discarded, rather than shipped back to the supplier. Mr. Fogg stated that his firm preferred to use only components made from ~~polypropylene~~, and that to avoid any of the problems associated with recycling, his firm did not ship rejected components (rejected during processing) back to the suppliers. Rejects are taken to the ~~Smith & Company~~ incinerator about ~~5~~ times a year for destruction. Mr. Fogg stated that his firm documented these destructions, and showed me the records coving the most recent destruction.

METROLOGY

Mr. Joseph DiRisio, QA Metrologist, stated he was responsible to Dr. Paul Turner for all the firm's metrology (measurement and calibration) operations. Mr. DiRisio stated he maintains the logs and records that show when equipment was last serviced, who serviced it, what the calibration errors are, if any, and when the next service calibration is scheduled. Each piece of production and testing equipment is assigned a unique number for calibration record purposes. As can be seen in Ex. 4, the firm has primary standards, for which calibration is recorded traceable to the National Bureau of Standards (NBS). Primary standards consist of transfer equipment such as weight sets, lengths, thermocouples and digital multi meters. These standards are calibrated by ~~Calibra Metrologist, Inc. White Plains, New York~~. Mr. DiRisio showed me the metrology manual and some of the records covering the servicing and calibration of equipment. Inspection revealed that the firm's laminar-flow hoods were serviced by ~~Lami Flow, Ltd. New York, New York~~ and that the firm has records to show that the hoods were serviced about every 6 months going back to 12/76. The most recent service was in 2/84.

~~POROSITY~~ STUDIES

The firm has an ongoing ~~porosity study program~~. Products from each day's production are tested for ~~porosity~~ by the firm's QC lab. Ex. 17, pages 23 and 24, are examples of the records for routine ~~porosity~~ testing. Mr. Fogg and Dr. Turner stated that routine ~~porosity~~ testing was a good QA procedure to establish a long term history of their products, and was much more valid than a one shot ~~porosity~~ study.

VALIDATION OF STERILIZATION

~~ETO~~ sterilization has always been performed by an outside contracted firm, ~~Minix Labs, Erie, PA~~. Mr. Fogg stated that ~~Minix~~ has never disclosed its ~~ETO~~ sterilization cycle parameters, feeling that such information was proprietary and that such information would not be released unless Cardio-Medical agreed not to make use of this information for its own purposes and agreed to release this information to any firm that might make use of this trade secret information. Mr. Fogg stated that Cardio-Medical was not able to agree to such a proposal. As such, Cardio-Medical asked ~~Minix Labs, Erie, PA~~ to conduct a validation study using Cardio-Medical's parameters, on Cardio-Medical's newest product, the IV fluid filter/air eliminator. This study is attached as Ex. 20, and was conducted in 1978. Mr. Fogg stated that this study determined that ~~ten to the minus 6~~ kill could be achieved in ~~14~~ hours using their parameters, and that, as a safety feature ~~Minix Labs~~ has been asked to sterilize Cardio-Medical's filters to the equivalence of ~~16~~ hours of Cardio-Medical's ~~ETO~~ sterilization parameters.

The sterilization validation study (Ex. 20) lists the parameters of the sterilization cycle (Pg. 1), the configuration of the test samples (Pg. 3), the protocol of the study (Pg. 1), the records and results of the study (Pages 8-34) and other information.

Mr. Fogg stated that his firm intended to discontinue using this contract sterilizer, and start using a sterilization procedure of their own, in about 6 months. Mr. Fogg stated that the proposed sterilization procedures would involve placing cartons of filters into each ~~3x2x1 foot aluminum orib. The orib would then be filled with 80% ETO, 20% mix. After 10 hours of exposure, the cartons would be removed from the orib and routed to the holding room for 24 hours~~. Mr. Fogg stated that his firm has been consulting with ~~Steri Consultant, Inc~~ and would be consulting with FDA's Dr. Bruch re this proposed ~~ETO~~ sterilization procedure, and methods to validate this procedure.

DEVICE HISTORY RECORDS

Device history records are maintained by sequential Cardio-Medical sterilization lot numbers. During this inspection, the most recently completed device history record available for review was for sterilization lot #340, for which the lot release report was signed on 5/29/84. Sterilization lot #340 contains the records for 26 lots ("day lots") of blood filters (see Pg. 17 of Ex. 17). Day lot #00441 was randomly picked as the device who's record I would review. Ex. 17 consists of most of the device history records relevant to sterilization lot #340, day lot #00441, which consists of records as follows:

PAGE	SUBJECT
1	Lot release report
2-4	Component Materials Record - lists the lot numbers of the components used in day lot #00441
5-13	Operation Cards - shows the who, what, when, and how many of each manufacturing step; and that the lot was divided into 9 tote boxes for easy handling
14-15	Forms Traceability
16	Inspection of Vacuum Bag Integrity
17	Material Movement Report - shows which pallet day lot #00441 was placed on, out of 4 pallets
18-19	In Process Testing Report - shows that day lot #00441 was subject to ~~porocity testing and USP/NF Bubble testing as well as LAL Pyrogen testing~~. The firm's ~~LAL pyrogen~~ testing procedure is described in Ex. 16.
20-22	QC Lab Book - shows the results of ~~Bubble Point testing~~
23-24	QC Lab Book - shows the results of ~~LAL~~ testing
25	Transfer Receiving Report - lists the products and quantities shipped to the contract sterilizer
26	QC Lab Book - shows the day lots of quantities which were designated for sterility testing by ~~Steri Consult, Inc., Boston, MA~~ and the day lots which were designated for pyrogen and safety testing by ~~Test All Ltd., Patterson, NJ~~
27	Letter, dated 5/1/84, directing ~~Steri Consult, Inc.~~ to test for pyrogens and safety
28	Letter, dated 5/1/84, directing ~~Steri Consult, Inc.~~ to test filters for sterility
29	Letter, dated 5/9/84, re: results of pyrogen testing
30	Letter, dated 5/12/84, re: results of safety and testing
31-32	Letter, dated 5/6/84, re: results of sterility testing
33	Final Inspection Record - inspection of lot after sterilization

DEVICE MASTER RECORD

During this inspection the firm's device master record for their Minipor Blood Filter was reviewed. Review of this record revealed that it contained, or referred to, almost all of the information required by the device GMPs (device specifications, manufacturing processes, quality assurance procedures, and packaging and labeling information). Only some minor deficiencies were noted. These are discussed under Objectionable Conditions. Information relevant to the device master record is contained in Exhibits 6 thru 16.

OBJECTIONABLE CONDITIONS

During this inspection the only objectionable conditions noted were some minor deficiencies in the device master record for the Minipor Blood Filters. These deficiencies were listed on an FD 483, Inspectional Observations, which was presented to and discussed with management at the close of the inspection.

Deficiencies noted were:

3. it does not list acceptance criteria for incoming components;

4. it does not list that components made of plastic are to receive an I.R. spectrographic analysis;

5. it does not list that the ~~cellulose acetate~~ filtering material is about ~~120~~ mesh, and it does not list the quantity of this material used to manufacture the blood filters;

6. the Operation Sheets have not been signed by all approving officials (Ex. II); and

7. the engineering diagrams for the housing, and top end caps do not bear the signature or initials of an approving corporate official (Ex. 12).

No other objectionable conditions were noted during this inspections.

MANUFACTURING CODES

The firm uses two manufacturing codes: a day lot code and a sterilization date code. The day lot code is a code that represents the date the product was manufactured (assembled). For example: "00441" means the 4th day of 1984, the 1st shift, where 004 if the fourth day, 4 is 1984, and 1 is the first shift. The sterilization date code "Jan 30 1984" is self explanatory.

The day lot code is ink stamped on every box and every carton, prior to ~~EtO~~ sterilization. The sterilization date code is ink stamped on every carton after the lot returns form ~~Ethylene Oxide~~ sterilization. The firm does not have a policy of coding the actual filter nor of coding the stick-on label applied to the filters.

CONSUMER COMPLAINTS

During this inspection the firm's consumer complaint file was reviewed, and a follow up was made of Medical Device Complaint M-00210 dated 5/31/84, which concerned leaking of Cardio Minipor IV Filter (no lot number given). Mr. Fogg stated that his firm had investigated this complaint and had determined that the hospital did not normally use their filters, and that the nurse that had registered the complaint was

not familiar with its use. A company representative visited the hospital and talked with the nurse about the application of the IV filter.

Mr. Fogg stated that the filter was designed for use at pressures under 600 mm of mercury, and that at above 600 mm of mercury the filer would crack in such a way as to maintain the integrity of solutions on the downstream side of the filter, and also prevent any air bubbles form getting into the system. M-00210 is attached as Exhibit 23, pages 5-8. The labeling for the IV filter specifically states that the filter is not to be used at above 600 mm pressure of mercury.

Review of the firm's complaint file revealed 10 complaints registered since 12/78 (excluding the above complaint), which the firm has assigned as number 91, 93, 94, 96, 97, 98, 100, 101, 102, and 103. Three complaints concerned Minipor blood filters, four complaints concerned blood dialysis filters, and three complaints concerned cardiovascular catheters concerning packaging defects, embedded particulate matter, cracks and leaks.

Mr. Fogg stated that all complaints are evaluated and investigated. Mr. Thomas Romano stated he evaluates all complaints to determine which department(s) should investigate the complaint. If available, sample of the subject lot are re-tested to determine if the complaint can be duplicated. Complaints are evaluated to determine if the complaint can be duplicated. Complaints are evaluated to determine if changes in QC or production procedures are needed, and to see if there are any patterns. Dr. Turner stated that during routine production, lots are subject to 100% checks and to a statistical check, in an effort to prevent any defects from leaving the plant. Mr. Romano stated that copies of complaints and the investigations are routinely routed to John Fogg, Dr. Paul Turner, and to William Pearl.

PROMOTION & DISTRIBUTION

Mr. Fogg stated that the firm distributes its filters nationwide, and overseas to Italy and Germany. Filters are sold to distributors who, in turn, sell the filters to hospitals. The firm's service representatives, both here and abroad, give lectures on the applications and proper use of Cardio-Medical's filters. Other promotion is performed by salesmen who work for the distributors.

Mr. Fogg provided some recent shipments as follows:

Invoice - And Date	Consignee	Number of Cases of Minipor IV Filters (8 each)
B8925 3/14/84	~~Mt. Saint Holly Hospital Canton, Ohio~~	20
B8845 3/2/84	~~Stainless Hospital Toledo, Ohio~~	80
B9045 3/28/84	~~Major General Hospital Boise, Idaho~~	60
B9051 3/29/84	~~VA Hospital Cardiac, Oklahoma~~	30
B9054 3/30/84	~~General Hospital Pleasure, Colorado~~	30
B9055 2/29/84	~~Molino Hospital Molino, Italy~~	20

B9058 3/30/84	~~Hurt Hospital~~ ~~Raine, North Dakota~~	30
B9069 4/2/84	~~Ritz Hospital~~ ~~Frankforth, Germany~~	10
B9076 4/2/84	Cardio General Hospital ~~Vein, South Dakota~~	10
B9082 3/29/84	~~Heart and Lung Clinic~~ ~~Dorothy, Kansas~~	20
W8474 3/16/84	~~Monitor Hospital~~ ~~Laser, Pennsylvania~~	20
D21606 3/30/84	~~St. Alchemy Hospital~~ ~~Cold, Vermont~~	15

The above invoices are attached as Ex. 25. The invoices are noted to reference the manufacturing (sterilization date. This date is ink stamped on each carton (case). This coding and invoice system will facilitate a recall, should one occur.

REFUSALS

There were no refusals during this inspection.

DISCUSSION WITH MANAGEMENT

At the close of the inspection, the FD 483, Inspection Observations, was presented to and discussed with Mr. John (NMI) Fogg, President. Dr. Paul M. Turner, Quality Assurance Manager, was also present during this discussion. Inspectional observations concerned five minor deficiencies in the device master record. Mr. Fogg stated the point #1, acceptance criteria for components, had already been corrected and gave me a copy of this document (see Ex. 8, Pg. 1). Mr. Fogg stated that the other deficiencies were simply oversights and could easily be corrected. No additional suggestions were given. One comment was made, which was that the firm discuss its proposed new ~~EtO~~ sterilization procedure with someone in the Center for Devices and Radiological Health, as this proposed procedure does not appear to have been commercially use. Mr. Fogg stated he believed a number of hospitals and small institutions were using this new ~~EtO~~ sterilization procedure, but was not aware of any manufacturer using the procedure.

SAMPLES

There were no samples collected during this inspection.

EXHIBITS

8. QC Manual re: policy & organization
9. QA manager responsibilities
   1. QC manager responsibilities
   2. Metrology manual
   3. Examples of calibration standards traceable to NBS
   4. List of components used to manufacture filters
   5. List of component suppliers
   6. Component sampling and acceptance plan
   7. Blood filter sampling & acceptance plan
   8. Component supplier agreements

9. Device master record operation sheets
10. Device master record
11. Sterility assurance procedures
12. ~~LAL~~ test procedures
13. Environmental air sampling procedures
14. ~~USP/NF bubble point~~ testing procedures
15. Device history record, blood filter, lot #00401, released 3/29/80
16. ~~EtO~~ residue study, 1976 & 1980
17. Safety/Toxicity study, 1976
18. EtO sterilization validation study, 1980
19. Letter, 2/1/84, from ~~Acme Sterilizers~~
20. Shelf life study plan, 1976
21. Consumer complaints
22. Medical device complaint M-00210, dated 5/31/84
23. Invoices of 12 recent shipments
24. List of devices manufactured
25. Labeling for blood filters

ATTACHMENTS

1. CP 7378.830 Systems analysis report
2. CP 7378.830A Sterile device compliance program pages 2-10 & 15-18

Thomas E. Cardamone
Investigator 800
New York District

MODEL WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

RESPONSIBLE INDIVIDUAL, TITLE
FIRM NAME
FIRM'S COMPLETE ADDRESS

Dear (Addressee),

During an inspection of your firm located in (City, State), on (dates), our Investigator(s) determined that your firm manufactures (type of device). (Name of device) are devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The above-stated inspection revealed that these devices are adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing, storage, or installation are not in conformance with the Good Manufacturing Practice (GMP) for Medical Devices Regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820, as follows:

1. Failure to conduct planned and periodic audits of the quality assurance program in accordance with written procedures. For example, no audits of the quality assurance program have been performed for at least 3 years.

2. Failure to investigate the failure of a device to meet performance specifications after a device has been released for distribution, and to make a written record of the investigation including conclusions and follow-up. For example, there are no records of failure investigations for Model _____, S/N _____, and Model _____, S/N _____, which were returned because they did not operate properly.

3. Failure to maintain device history records for Model _____ to demonstrate that the devices are manufactured in accordance with the device master record.

4. Failure to immediately review, evaluate and investigate any complaint pertaining to injury, death, or any hazard to safety. For example, there is no record of the investigation of a report that a child's death associated with the use of Model _____ at the Community Medical Ctr. on/or about Feb. 8, 1991.

Additionally, the above stated inspection revealed that your devices are misbranded within the meaning of Section 502(t)(2) of the Act, in that your firm failed to submit information to the Food and Drug Administration as required by the Medical Device Reporting (MDR) Regulation, as specified in 21 CFR Part 803. Specifically, you failed to submit an MDR report to FDA after receiving information which reasonably suggested that one of your commercially distributed devices may have caused or contributed to a death. The February 8, 1991, incident report from the Community Medical Center in which a child standing in a crib fell over, caught his head in a "Y" formed by the crib rail and end post, and died, should have been reported as a death.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA 483 issued at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you shall promptly initiate permanent corrective actions.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket submissions for devices to which the GMP deficiencies are reasonably related will be cleared until the violations have been corrected. Also, no requests for Certificates For Products For Export will be approved until the violations related to the subject devices have been corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office in writing within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to (Name), Compliance Officer, Food and Drug Administration, (City, State & Zip Code).

Sincerely yours,

update: A. Lowery, 8-93
update: J. Puleo & A. Lowery, 5-9-96
edited: N. Freeman, 5/13/96
edited: J. Strojny, 5/15/96
edited: T. Cardamone, 6/21/96
revised: K.Trautman, 7/96
edited: J. Strojny, 8-13 **Word Searches: chapter, U.S. Designated Agent, GMP, regulation, QS, firm, guideline; K. Trautman comments included**
edited: T. Cardamone, 8-15
edited: J. Strojny, 9-9 Quality System = QS after 1st reference

19 APPENDIXES

QUALITY SYSTEMS REGULATION.....xxappdx1.zip

APPLICATION OF THE MEDICAL DEVICE GMPS TO COMPUTERIZED DEVICES AND MANUFACTURING PROCESSESxxappdx2.zip

In the electronic version - the above files are stored in zipped format to save disk space.

The above files are located on this disk and must be expanded using Pkware unzip or similiar file expansion software.

<HEAD>

<TITLE>Text Version of the CGMP</TITLE>

</HEAD>
<BODY>
<IMG SRC = "newtst.gif">

<H1>Text Version of the CURRENT GOOD MANUFACTURING PRACTICE (CGMP) FINAL RULE</H1>
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<P>
<HR>
<P>
<P>
<CENTER> <H2>WORKING DRAFT OF THE CURRENT GOOD MANUFACTURING PRACTICE (CGMP) FINAL RULE</H2>
</CENTER>
<PRE>

July 1995
Office of Compliance
Center for Devices and Radiological Health
U.S. Food and Drug Administration
2098 Gaither Road
Rockville, MD 20850

Table of Contents

<A NAME="1">NOTICE OF AVAILABILITY</A>

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

21 CFR Part 820
[Docket No. 90N-0172]
RIN No. 0905-AD59

Medical Devices; Working Draft of the Current Good Manufacturing Practice (CGMP) Final Rule; Notice of Availability; Request for Comments; Public Meeting

AGENCY: Food and Drug Administration, HHS.
ACTION: Notice of availability and announcement of public meeting.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a working draft of a final rule on the revision of the current good manufacturing practice (CGMP) regulation for devices (quality system regulation). The quality system regulation includes requirements related to the methods used in and the facilities and controls used for: Designing, purchasing, manufacturing, packaging, labeling, storing, installing, and servicing of medical devices intended for human use. The working draft contains a number of changes made in response to the many comments received on the proposal to amend the CGMP regulation, and it represents the agency's view of the necessary elements of a CGMP regulation. In this document, FDA is also announcing a public meeting to be held on the working draft. At a later time, FDA will announce a meeting of the Device Good Manufacturing Practice Advisory Committee. The publication of this document is intended to make the working draft of the quality system regulation available to the public in order to give those who will attend the public meetings the opportunity to be informed of the agency's current thinking on the final rule and to allow interested parties an additional opportunity to comment before a final regulation is issued.

DATES: The public meeting will be held on Wednesday, August 23, 1995, from 9 a.m. to 4:30 p.m. Should more time be needed, Thursday, August 24, 1995, has been set aside for this purpose. Interested persons, whether or not they are able to attend, may submit written comments on the issues described in this notice by (insert date 90 days after date of publication in the Federal Register). Submit written notices of participation on or before (insert date 15 days after date of publication in the Federal Register). Any final regulation that may issue, after a thorough review of the comments received on this working draft, will become effective 180 days following its publication in the Federal Register. A transcript of the meeting will be available from the Dockets Management Branch (address below).

ADDRESSES: The meeting will be held at the Parklawn Bldg, conference room D, 5600 Fishers Lane, Rockville, MD. There is no registration fee for this meeting. Submit written requests to make a presentation at the meeting to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. Submit written requests for single copies of the working draft of the quality system regulation to the Division of Small Manufacturers Assistance (HFZ-220),

Food and Drug Administration, 1350 Piccard Dr., Rockville, MD 20850. Send two self-addressed adhesive labels to assist the office in processing your request. Submit written comments on the working draft to the Dockets Management Branch (HFA-305) (address above). Requests and comments should be identified with the docket number found in brackets in the heading of this document. A copy of the working draft and received comments are available for public examination in the Dockets Management Branch between 9 a.m. to 4 p.m., Monday through Friday. Copies of a facsimile of the working draft, totaling approximately 230 pages (approximately 190 pages of draft preamble and 40 pages of draft regulation), are available from CDRH Facts on Demand (1-800-899-0281). Copies of the revision may also be obtained from the electronic docket

administered by the Division of Small Manufacturers Assistance and are available to anyone with a video terminal or personal computer (1-800-252-1366).

FOR FURTHER INFORMATION CONTACT: Kimberly A. Trautman, Office of Compliance, Center for Devices and Radiological Health (HFZ-341), Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850, 301-594-4648.

SUPPLEMENTARY INFORMATION:

I. Background

Manufacturers establish and follow quality systems to help ensure that their products consistently meet applicable requirements and specifications. The quality systems for FDA regulated products (food, drugs, biologics, and devices) are known as CGMP's. CGMP requirements for devices (part 820 (21 CFR part 820)) were first authorized by section 520(f) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(f)), which was among the authorities added to the act by the Medical Device Amendments of 1976 (Pub. L. 94-295). The Safe Medical Devices Act (the SMDA) of 1990 (Pub. L. 101-629), enacted on November 28, 1990, amended section 520(f) of the act, providing FDA with the explicit authority to add preproduction design validation controls to the CGMP regulation. The SMDA also added a new section 803 to the act (21 U.S.C. 383) which, among other things, encourages FDA to work with foreign countries toward mutual recognition of CGMP requirements.

FDA undertook the revision of the CGMP regulation in part to add the design controls authorized by the SMDA to the CGMP regulation, and in part because the agency believes that it would be beneficial to the public, as well as the medical device industry, for the CGMP regulation to be consistent, to the extent possible, with the requirements for quality systems contained in applicable international standards, namely, the International Organization for Standards (ISO) 9001:1994 "Quality Systems - Model for Quality Assurance in Design, Development, Production, Installation, and Servicing" (Ref. 1), and ISO working draft revision of ISO/DIS 13485 "Quality Systems - Medical Devices - Supplementary Requirements to ISO 9001" (Ref. 2), among others. The preamble to the November 23, 1993, proposal contains a detailed discussion of the history of the device CGMP regulation, from the agency's initial issuance of the regulation through FDA's decision to propose revising the regulation.

The agency's working draft embraces the same "umbrella" approach to CGMP regulation that is the underpinning of the existing CGMP regulation. Thus, because this regulation must apply to so many different types of devices, the regulation does not prescribe in detail how a manufacturer must produce a specific device. Rather, the regulation lays the framework that all manufacturers must follow, requiring that the manufacturer develop and follow procedures, and fill in the details, that are appropriate to a given device according to the current state-of-the-art manufacturing for that specific device. FDA has made further changes to the proposed regulation, as the working draft evidences, to provide manufacturers with even greater flexibility in achieving the quality requirements.

II. Decision to Make a Working Draft Available for Comment

On November 23, 1993 (58 FR 61952), the agency issued the proposed revisions to the CGMP regulation, entitled "Medical Devices; Current Good Manufacturing Practice (CGMP) Regulations; Proposed Revisions; Request for Comments," and public comment was solicited. After the proposal issued, FDA met with the Global Harmonization Task Force (GHTF) Study Group in early March 1994, in Brussels, to compare the provisions of the proposal with the provisions of ISO 9001:1994 and European Norm (EN) standard EN 46001 "Quality Systems - Medical Devices - Particular Requirements for the Application of EN 29001". The GHTF includes: Representatives of the Canadian Ministry of Health and Welfare; the Japanese Ministry of Health and Welfare; FDA; and industry members from the European Union, Australia, Canada, Japan, and the United States. The participants at the GHTF meeting favorably regarded FDA's effort toward harmonization with international standards. The GHTF submitted comments, however, noting where FDA could more closely harmonize to achieve consistency with quality system requirements worldwide. Since the proposal published, FDA has also attended

numerous industry and professional association seminars and workshops, including ISO Technical Committee 210 "Quality Management and Corresponding General Aspects for Medical Devices" meetings, where the proposed revisions were discussed.

The original period for comment on the proposal closed on February 22, 1994, and was extended until April 4, 1994. Because of the heavy volume of comments and the desire to increase public participation in the development of the quality system regulation, FDA decided to publish this notice of availability in the Federal Register to allow comment on the working draft, to be followed by two public meetings, as describe below, before issuing a final regulation.

This working draft represents the agency's current views on how it would respond to the many comments received, and on how the agency believes a final rule should be framed. FDA solicits public comment on this working draft to determine if the agency has adequately addressed the many comments received and whether the agency has framed a final rule that achieves the public health goals to be gained from implementation of quality systems in the most efficient manner.

III. Opportunity for Public Meeting

FDA intends to hold two public meetings on the revision of the quality system regulation. One meeting, which will be held pursuant to 21 CFR part 10.65(b), is scheduled for August 23, 1995. Interested persons who wish to participate in the public meeting may, on or before (insert date 15 days after date of publication in the Federal Register) submit a written notice of participation to the Dockets Management Branch (address above). All notices submitted should be identified with the docket number found in brackets in the heading of this document and should be clearly marked "Notice of Participation". The notice should also contain the name, address, telephone number, business affiliation of the person requesting to make a presentation, a brief summary of the presentation, and the approximate time requested for the presentation.

Individuals or groups having similar interests are requested to consolidate their comments and present them through a single representative. FDA may require joint presentations by persons with common interests. FDA will allocate the time available for the meeting among the persons who properly submit a written notice of participation. The meeting is informal, and the rules of evidence do not apply.

Because of the complexity of the issues to be discussed at the public meeting, FDA has concluded that it would not be beneficial to the meeting participants or the agency to devote the entire meeting to public presentations. Therefore, after reviewing the notices of participation and accompanying information, FDA will schedule each appearance and notify each participant by mail or telephone of the time allotted to the person and the approximate time the person's presentation is scheduled to begin. Each presentation will be limited in time in order to provide sufficient time for prepared presentations by the agency followed by a discussion period. The schedule of the public meeting will be available at the meeting, and later it will be placed on file in the Dockets Management Branch (address above).

Individuals and organizations that do not submit a notice of participation but would like to testify will have the opportunity, if time permits. A transcript of the proceedings of the public meeting, as well as all data and information submitted voluntarily to FDA during the public meeting to discuss the working draft, will become part of the administrative record and will be available to the public under 21 CFR 20.111 from the Dockets Management Branch (address above).

While oral presentations from specific individuals and organizations will be limited during the public meeting, the written comments submitted as part of the administrative record may contain a discussion of any issues of concern. All relevant data and documentation should be submitted with the written comments.

There will also be a public meeting with the Device GMP Advisory Committee, established under section 520(f)(1)(B) of the act, on the working draft. That meeting will be governed by part 14 (21 CFR part 14) of FDA's administrative practices and procedures regulations, which specifies the requirements for filing notices of appearance. The tentative dates for the meeting are September 13 and 14, 1995. A notice of the exact dates, time, and place for the meeting will appear in a future issue of the Federal Register. After considering the written comments and the views expressed at the public meeting and at the September advisory committee meeting, FDA will publish a final rule in the Federal Register.

IV. References

The following information has been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday:

(1) ISO 9001:1994 "Quality Systems - Model for Quality Assurance in Design, Development, Production, Installation, and Servicing."

(2) ISO working draft revision of ISO/DIS 13485 "Quality Systems - Medical Devices - Supplementary Requirements to ISO 9001."

V. Comments

Interested persons may, on or before (insert date 90 days after date of publication in the Federal Register), submit to the Dockets Management Branch (address above), written comments regarding this working draft. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The working draft and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

<A NAME="11">WORKING DRAFT OF THE CGMP FINAL RULE - PREAMBLE</A>

Approximately 280 separate individuals or groups commented on the proposal published in the Federal Register on November 23, 1993. Of the comments received, many were quite constructive and addressed numerous provisions of the proposal. Most of the changes made from the proposal to the tentative final were made either in response to specific comments or to better harmonize FDA requirements with international standards, as many commentors generally requested. FDA's response to the comments received on the proposal and explanations for the changes made from the proposal follow.

<A NAME="pSubpart A">A. General Provisions (Subpart A)</A>

i. Scope

1 The title of the regulation, as reflected in this subsection, has been changed from the "Current Good Manufacturing Practices (CGMP)" regulation to the "Quality System" regulation. This revision follows the suggestion underlying many comments on specific provisions that FDA generally harmonize the CGMP requirements and terminology to international standards. Both ISO 9001 and EN 46001 employ this terminology to describe the CGMP requirements. In addition, this title accurately describes the sum of the requirements, which now include the current good manufacturing practice requirements for design, purchasing, and servicing controls. CGMP requirements now cover a full quality system.

FDA notes that the requirements embodied in this Quality System regulation have been accepted worldwide as necessary to ensure that acceptable products are produced. While the regulation has been harmonized with the medical device requirements in the EU and the requirements proposed by Japan and Canada, it is anticipated that other countries will adopt similar requirements in the near future.

2 Several comments expressed that section 820.1(a)(1) should not state that the regulation establishes the "minimum" requirements because that implies that compliance with the stated requirements may be insufficient. They suggested that FDA delete the word "minimum," therefore, to avoid auditors searching for additional requirements.

FDA does not believe that the provision would have required that manufacturers meet additional requirements not mandated by the regulation, but has modified the section to clarify its intent by stating that the regulation establishes the "basic" requirements for manufacturing devices. The Quality System regulation provides a framework of basic requirements for each manufacturer to use in establishing a quality system appropriate to the devices manufactured and manufacturing processes employed. Manufacturers must adopt current and effective methods and procedures specific to each device they manufacture to comply with and implement the basic requirements. The regulation provides the flexibility necessary to allow manufacturers to adopt advances in technology, as well as new manufacturing and quality system procedures as they become available.

During inspections, FDA will examine such procedures to assess whether a manufacturer has established procedures and followed requirements that are appropriate to a given device under the current state-of-the-art manufacturing for that specific device. FDA investigators receive extensive training to ensure uniform interpretation and application of the regulation to the medical device industry. Thus, the agency does not believe that FDA inspectors will cite deviations from requirements not contained in this part. However, as noted above, FDA has altered the language of the scope to make clear that additional, unstated requirements do not exist.

3 A few comments suggested eliminating the distinction between critical and noncritical devices, thus eliminating the need for requirements distinct to critical devices. Other comments disagreed, asserting that eliminating the distinction would increase the cost of production without improving the safety and

effectiveness of low risk devices.

FDA agrees in part with the comments that suggest eliminating the distinction between critical and noncritical devices and has eliminated the term "critical device" from the scope, definitions, and regulation in sections 820.65, "Critical devices, traceability" and 820.165, "Critical devices, labeling." However, FDA has retained the concept of distinguishing between devices for the proposed traceability requirements in section 820.65. As addressed in the discussion under that section, FDA believes that it is imperative that manufacturers be able to trace, by control number, any device where such requirements are necessary to assure the protection of the public health.

The deletion of the terminology will bring the regulation in closer harmony with International Organization for Standards (ISO) 9001:1994 "Quality Systems - Model for Quality Assurance in Design, Development, Production, Installation, and Servicing" and the quality systems standards or requirements of other countries.

Finally, FDA notes that eliminating the term "critical device" and the list of critical devices does not result in the imposition of many more requirements that are not already being followed by a majority of the medical device industry.

4 Several comments recommended that the short list of Class I devices subject to design control requirements be deleted from the regulation and be placed in the preamble, to allow additions or deletions without requiring a change to the entire regulation.

FDA disagrees that the list of devices subject to design control requirements should be deleted from the regulation.
Placing the list in the regulation establishes the requirements related to those devices, and is convenient for use by persons not familiar with, or who do not have access to, the preamble. Further, FDA notes that individual sections of a regulation may be revised independent of the remainder of the regulation. If the list is revised, FDA will notify each known manufacturer by letter that FDA has determined that the design control requirements apply, or no longer apply, to a device.

5 Many comments stated that application of the regulation to component manufacturers would increase product cost, with questionable value added to device safety and effectiveness, and that many component suppliers would refuse to supply components or services to the medical device industry. This would be especially likely to occur, it was suggested, where medical device manufacturers account for a small fraction of the supplier's sales.

FDA believes that because of the complexity of many components used in medical devices, their adequacy cannot always be assured through inspection and test at the finished device manufacturer. This is especially true of software and software related components, such as microprocessors and microcircuits. Quality must be designed and built into components through the application of proper quality systems.
Further, FDA has encountered manufacturers who have conducted little or no incoming tests or inspections on "critical" components and subassemblies because they were produced at their "sister facility." These manufacturers also attempted to preclude FDA from conducting CGMP inspections, claiming that the subsidiaries were component manufacturers and that FDA could only inspect the final assembly aspect.

However, FDA notes that the Quality System regulation now explicitly requires that the finished device manufacturer assess the capability of suppliers, contractors, and consultants to provide quality products pursuant to section 820.50, "Purchasing controls." These requirements supplement

the acceptance requirements under section 820.80. Manufacturers must comply with both sections for any incoming component or subassembly, or service received, regardless of the finished device manufacturer's financial or business affiliation with the person providing such products or services. FDA believes that these purchasing controls will provide additional assurance that suppliers, contractors, and consultants have adequate controls to produce acceptable components.

Therefore, balancing the concerns of the medical device industry and the agency's public health and safety concerns, FDA has decided to retain the provision making the CGMP regulation applicable to those component manufacturers who manufacture components specifically for use in a medical device, but state its intention not to regularly inspect such manufacturers. The agency will inspect component manufacturers only in rare instances, where it determines that such inspection is necessary to assure the safety and effectiveness of the device.

Instead, FDA will continue to focus its inspections on the finished device manufacturer, and expects that such manufacturer will properly ensure that the components it purchases are safe and effective. In this regard, the agency emphasizes that test and inspect methods may not be sufficient to assure acceptability for certain components, and the finished device manufacturer may be required to ensure that its suppliers are in fact complying with relevant CGMP provisions. FDA is also putting finished device manufacturers on notice that the failure to comply with both sections 820.50 and 820.80 will result in enforcement action.

6 One comment stated that the proposed section 820.1(a)(2) should be revised to include the District of Columbia and the Commonwealth of Puerto Rico, as written in the current regulation.

FDA agrees with the comment. These localities were inadvertently omitted and have been added to the regulation.

7 Some comments on proposed section 820.1(c) recommended that the section be deleted as it already appears in the act and does not allow for minor deviations from the regulation. Others stated that the provision implies that FDA will subject devices or persons to legal action, regardless of the level of noncompliance. Still others suggested that only intentional violations of the regulation should give rise to regulatory action.

FDA disagrees with all of these comments. The consequences of the failure to comply, and the legal authority under which regulatory action may be taken, should be written in any regulation so that the public may be fully apprised of the possible results of noncompliance, and understand the importance of compliance. FDA notes that the agency exercises discretion when deciding whether to pursue a regulatory action and does not take enforcement action for every violation it encounters. Further, FDA generally provides manufacturers with warning prior to initiating regulatory action, and encourages voluntary compliance. The agency also notes, however, that violations of this regulation need not be intentional to place the public at serious risk, or for FDA to take regulatory action for such violations.

In response to the concerns regarding the tone of the section, however, the title has been renamed and the proposed section amended to explicitly state the legal authority under which the regulation is promulgated, as well as the legal authority related to noncompliances.

FDA has also deleted the specific provisions described in the section with which the failure to comply would render the devices adulterated. The term "part" includes all of the regulation's requirements.

8 A few comments on proposed section 820.1(c)(2) requested that the agency clarify what FDA meant by requiring that foreign manufacturers "schedule" an inspection. Others stated that the proposed language would prohibit global harmonization because it would limit third party audits in place of FDA inspections.

FDA has moved the provision related to foreign manufacturers into a separate section and has modified the language. The agency believes that it is imperative that foreign facilities be inspected for compliance with this regulation and that they be held to the same high standards to which U.S. manufacturers are held. Otherwise, the U.S. public will not be sufficiently protected from potentially dangerous devices and the U.S. medical device industry will be at competitive disadvantage.

FDA intends to schedule inspections of foreign manufacturers in advance to ensure availability due to varying holidays and shut down periods. However, the language pertaining to the "scheduling" of such inspection is deleted to allow flexibility in scheduling methods.

FDA disagrees that, as written, the language would prohibit inspections by third parties. FDA may use third party inspections, as it uses other compliance information, in setting its priorities and utilizing its resources related to foreign inspections. In this regard, FDA looks forward to entering into agreements with foreign countries related to CGMP inspections, where appropriate, that would provide FDA with reliable inspectional information.

9 Two comments stated that the section on "Exemptions and variances," now section 820.1(e), should require that FDA provide a decision on petitions within sixty (60) days of receipt and state that the agency will take no enforcement action with respect to the subject of the petition until a decision is rendered. The comments said that the petition process is long and arduous, and not practical.

FDA disagrees with the comments. Currently, FDA is required by section 520(f)(2)(B) of the act (21 U.S.C. 360j(f)(2)(B)) to respond within 60 days of receipt of the petition. When the 1978 CGMP regulation was published, there was a prediction that FDA would be overwhelmed with petitions for exemption and variance from the regulation. Over the past fifteen (15) years, since the CGMP regulation first became effective, FDA has only received approximately 75 petitions. It is FDA's opinion that few petitions have been received because of the flexible nature of the language of the CGMP regulation. FDA has attempted to write the current regulation with at least the same degree of flexibility, if not more, to allow manufacturers to design a quality system that is appropriate for their device and operations that is not overly burdensome.

Guidelines for the submission of petitions for exemption or variance are available from the Division of Small Manufacturers Assistance. The petition guidelines state that FDA will not process a petition for exemption or variance while an FDA inspection of a manufacturer is ongoing. Until FDA has approved a petition for an exemption or variance, a manufacturer should not deviate from the requirements of this regulation. FDA must first have the opportunity to ensure that the manufacturer has established that an exemption or variance is warranted, to carry out its obligation of ensuring that devices are safe and effective.

10 Several comments stated that the proposed requirements were not necessary for all manufacturers, particularly small manufacturers with few employees and low risk devices. Other comments stated that the documentation requirements were excessive.

FDA generally disagrees with these comments. The provisions of the regulation are considered to be the "basic" requirements for the design and manufacture of medical devices. And, as noted in the previous response, the requirements are written in general terms to allow manufacturers and designers to establish procedures appropriate for their device and operations. Because the regulation requirements are basic, they will apply in total to most manufacturers subject to the

regulation. However, the extent of the documentation necessary to meet the regulation requirements may vary with the complexity of the design and manufacturing operations, the size of the firm, the importance of a process, and the risk associated with the failure of the device, among other factors. Small manufacturers may design acceptable quality systems that require a minimum of documentation and, where possible, automate documentation. In many situations, documentation may be kept at a minimum by combining many of the recordkeeping requirements of the regulation, for example, the production SOPs, handling, and storage procedures.

When manufacturers or designers believe that the requirements are not necessary for their operation, they may petition for an exemption or variance from all or part of the regulation pursuant to section 520(f)(2) of the act. In addition, FDA has added a similar variance provision in section 820.1(e)(2) which the agency can initiate where it determines that such variance is in the best interest of the public health. Under this provision, for instance, the agency may initiate and grant a variance to manufacturers of devices during times of product shortages, where the devices are needed by the public and may not otherwise be made available, where such manufacturers can adequately assure that the manufacture of the devices is likely to result in a safe and effective device.

The agency envisions this provision as a bridge, providing a manufacturer the time necessary to allow it to fulfill the explicit requirements in the regulation while providing an important and needed device to the public. Thus, the variance would only be provided for a short period of time, and then only when the device remained necessary and in short supply. Under this provision, FDA will require a manufacturer to submit a plan detailing the action it is taking to assure the safety and effectiveness of the devices it manufactures and to meet the requirements of the regulation.

This agency initiated variance provision is in accordance with section 520(f) of the act (21 U.S.C. 360j(f)) which permits, but does not require, FDA to promulgate regulations governing the good manufacturing practices for devices and section 701(a) (21 U.S.C. 371(a)), which permits FDA to promulgate regulations for the efficient enforcement of the act. Because the statute does not mandate that the agency establish any requirements for device GMP, the agency has the authority to determine that the manufacturers of certain devices need not follow every requirement of the regulation.

Further, the agency initiated variance provision is in keeping with the intent of Congress that FDA prevent hazardous devices from reaching the marketplace, H.R. Rep. No. 853, 94th Cong., 2d Sess. 25-26 (1976), and the general intent of the act that the agency undertake to protect the public health, in that the agency will only initiate such a variance where the devices are needed and may not otherwise be made available and the manufacturer can assure the agency that its procedures are likely to be adequate and that it is actively pursuing full compliance, and the variance will only be in effect for a limited time.

Proposed section 820.1(e) has been modified to include the above addition, to reflect the title change of the regulation, and to provide the most current address for the Division of Small Manufacturers Assistance.

ii. Definitions

1 Several comments were received regarding the definition of "complaint." Commentors generally believed that the definition was unclear and could be interpreted to include routine service requests, communications from customers unrelated to the quality, safety, or effectiveness of the device, and internal communications.

FDA agrees with the comments in part and has modified the definition to make clear that communication from any of the sources mentioned in the comments would be considered a "complaint," but only if the communication alleged some deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the device. The definition is now very similar to the definition used in the ISO working draft revision of ISO/DIS 13485 "Quality Systems - Medical Devices - Supplementary Requirements to ISO 9001."

The regulation addresses service requests and in-house indications of dissatisfaction under section 820.100, "Corrective and preventive action." This section requires manufacturers to establish procedures to identify quality problems and process the information received to detect and correct quality problems. Information generated in-house relating to quality problems should be documented and processed as part of this corrective and preventative action program as well.

With respect to service requests, section 820.200, "Servicing" states that any service report relating to or concerning a death, injury, or hazard to safety shall be considered a complaint and processed in accordance with section 820.198, "Complaint files." All other service reports must be analyzed for trends or systemic problems and when found, these trends or systemic problems must be investigated according to the provisions of section 820.100, "Corrective and preventive action."

2 One comment suggested that the agency delete the phrase, "used during device manufacturing" in the definition of "component" because it was confusing and may cause problems with certain aspects of distributor operations.

FDA agrees and has deleted the words "used during device manufacturing" from the definition since it was not intended to differentiate between distributors and manufacturers.

3 Several comments stated that the term "complete history" in the definition of "control number" should be clarified or deleted in that it was unclear what a complete production history was, and the term could be construed to require full traceability for all component lots of any product containing a control number.

FDA disagrees. The control number is the means by which the history of the device, from purchase of components and materials through distribution, may be traced, where traceability is required. The definition does not require that a manufacturer be able to trace the device whenever control numbers are used. In fact, the definition itself does not establish any requirements. The agency notes, however, that the manufacturer's traceability procedures should ensure that a complete history of the device, including environmental conditions which could cause the device to fail to conform to its specified requirements, can be traced and should facilitate both investigation of quality problems and corrective action. FDA also notes that the term "complete history" is contained in the current definition of "control number," which has been part of the CGMP regulation for the past 15 years. The agency is not aware of any misinterpretation of the definition. Therefore, FDA has retained the term "complete history" in the definition.

FDA has, however, amended the definition for added flexibility, to state that symbols may be used, and has included the term "unit" for any device that is not manufactured as a lot or batch.

4 The definition of "critical device" has been deleted for the reasons discussed above.

5 Several comments stated that the term "design history record" should be changed because the acronym for the term was the same as that for device history record. Other comments said the "design history record" should not need to contain documentation of a "complete" design history. One comment stated that the definition should allow reference to records containing the design history of the device. A few comments stated that the term should be deleted altogether because

it was redundant with the definition of device master record (DMR).

FDA agrees in part with these comments and has changed the term "design history record" to "design history file." In addition FDA has amended the provisions to require that the file describe the complete design history, as it may not be necessary to maintain a record of every step in the design phase, although the whole history should be apparent from the document. In addition, sufficient records must be maintained, or referenced in the file, to verify that the design was developed in accordance with the design and development plan and other applicable design requirements of the regulation.

FDA does not agree that the definition of the design history file and DMR are redundant. The design history file should include, for example, the design and development plan, design review results, and design validation and verification results, as well as any other data necessary to establish compliance with the design requirements. The DMR contains all of the procedures related to a specific device established as required by this part and the most current manufacturing specifications of the device, once the design specifications have been transferred into production.

6 Two comments stated that the definition of "design output" should be revised because it should not be necessary, and would be burdensome, to keep records of and review the "results of a design effort at each design phase and at the end." Other comments suggested that the design output definition should be restricted to physical characteristics of the device.

FDA agrees in part, but has not deleted the phrase "results of a design effort at each design phase and at the end" from the definition. The intent was not to dictate when design phases would occur. Such phases will be defined in the design and development plan. For example, a manufacturer may only have one design phase for a new type of syringe. Thus, design output would constitute the results of that one effort. The results of each design phase constitute the total design output. The definition has been amended, however, to clarify that the final design output becomes the basis for the device DMR and is not merely a duplication of records.

FDA disagrees with the comments that suggest that the design output should be restricted to physical characteristics of the device. Design output is more than just the device specifications, but includes, among other things, the specifications for the manufacturing process, the quality assurance testing, and the device packaging and labeling. It is important to note that the design effort should not only control the design aspects of the device itself, but everything about the device from the initial determination to develop the design, through manufacturing and distribution, until the end of life of the device.

7 A few comments received on the definition of "design review" stated that proposing solutions to problems was not the role of the design review activity. Two other comments expressed concern that the definition would require that each design review be "comprehensive."

In response to the comments on the proper role of design review, FDA agrees that the design review function is typically not responsible for establishing solutions, although it may do so in many small operations. The definition has been amended to make clear that the design review need not propose actual solutions, but should propose that solutions to any problems discovered be developed.

Regarding the scope of each design review, each design review need not be "comprehensive" for the entire design process but must be "comprehensive" for the design phase being reviewed. However, at the end of the design process when the design is transferred to production, all aspects of the design process should have been reviewed.

A few other changes were made to harmonize with the definition in ISO 8402:1994 "Quality - Vocabulary."

8 Comments on the definition of "device master record" pointed out that the definition is not consistent with the requirements of section 820.181, "Device master record." Other comments stated that the definition should allow the reference to records at some location.

FDA agrees with the comments that found the DMR definition and requirements to be inconsistent and has amended the definition to be consistent with the requirements set forth in section 820.181. FDA does not believe, however, that it is necessary to modify the definition to include the referencing of records because the DMR requirements in section 820.181 state that the DMR "shall include or refer to the location of" the required information.

9 The definition for the term "end-of-life" was added because this term is used in the definitions for "refurbisher" and "servicing" to help distinguish the activities of refurbishing from those of servicing. FDA determined that such a distinction was necessary, due to comments and ongoing confusion regarding the difference between the two functions, and the different requirements applicable to the functions.

FDA was unable to find an adequate definition of servicing and refurbishing in any national or international standards documents that adequately differentiated between the two. Therefore, in an effort to distinguish what is considered to be repairable or serviceable, from what is considered to be nonrepairable or requiring refurbishing, FDA has used the term "end-of-life," in both the servicer and refurbisher definitions. Prior to the end-of-life, repair or maintenance is servicing. At the end of life, the device is rebuilt by a refurbisher. When a person refurbishes a device, he becomes the "original device manufacturer" for the refurbished device.

10 The few comments received on the definition of "establish" indicated a concern that the regulation would require too much documentation and be more onerous than ISO 9001 requirements.

FDA disagrees. The term is only used where documentation is necessary. FDA also notes that the quality system regulation is premised on the theory that adequate written procedures, which are implemented appropriately, will likely ensure the safety and effectiveness of the device. ISO 9001:1994 relies on the same premise. The 1994 version of ISO 9001 broadly requires the manufacturer to "establish, document, and maintain a quality system," which includes documenting procedures for meeting the requirements.

The definition has been amended, however, in response to general comments received, to clarify that a "document" may be written or electronic, allowing flexibility for any type of recorded media.

11 FDA received comments questioning the addition of the wording that a "finished device" includes a device that is intended to be sterile, but that is not yet sterile.

FDA disagrees with the comments, but has amended the definition to clarify its position. Since the 1978 CGMP regulation was promulgated, FDA has been questioned repeatedly regarding whether devices intended to be sold as sterile are considered subject to the CGMP requirements, even though they have not yet been sterilized. The agency had intended the new definition to make explicit the application of the regulation to the manufacture of sterile devices that have yet to be sterilized. Although FDA believes it should be obvious that such devices are subject to CGMP requirements, some manufacturers have taken the position that the regulation does not apply because the device is not "finished" or "suitable for use" until it has been sterilized.

To better clarify its intent, FDA has amended to definition to add that all devices that are capable of functioning, including those devices that could be used even though they are not yet in their final form, are "finished devices." Thus, devices that are intended to be sterilized, polished, inspected and tested, or packaged or labeled by a purchaser/manufacturer, among other activities, are finished devices prior to the completion of such activity.

The distinction between "components" and "finished devices" was not intended to permit manufacturers to manufacture devices without complying with CGMP requirements by claiming that other functions, such as sterilization, incoming inspection (where sold for subsequent minor polishing, sterilization, or packaging), or insertion of software, will take place. The public would not be adequately protected were this the case, as any manufacturer could claim that a device was not a "finished" device subject to the CGMP regulation because it was not in its "final" form. This problem should be lessened with the application of the regulation to components manufactured specifically for use as part of a medical device.

The term "for commercial distribution" was deleted from the definition of "finished device" because it is not necessary for a device to be in commercial distribution to be considered a finished device.

12 Two comments on the definition of "lot or batch" requested that the definition be clarified: one to reflect that single units may be produced for distribution, the other to indicate that what constitutes a lot or a batch may vary depending on the context.

In response to the comments, FDA has modified the definition to make clear that a lot or batch may, depending on circumstances, be comprised of one component or finished device. Whether for inspection, or distribution, a lot or batch is determined by the factors set forth in the definition; of course, a manufacturer may determine the size of the lot or batch, as appropriate.

13 Several comments received on the definition of "executive management" objected that the definition is inconsistent with ISO 9001. Others thought that FDA should better define the level of management the term was intended to define.

FDA agrees with both concerns and has modified the definition by deleting the second half, which appeared to bring executive authority and responsibility too far down the organization chart. The term was intended to apply only to management that has the authority to bring about change in the quality system and the management of the quality system. Although such management would clearly have authority over, for example, distribution, those who may have delegated management authority over distribution would not necessarily have authority over the quality system and quality policy. Accordingly, the definition has been modified to include only those who have the authority and responsibility to establish and make changes to the quality policy and quality system. It is the responsibility of top management to establish and communicate the quality policy, as defined in section 820.3(v), "quality policy," regardless of whether specific functions are delegated. In addition, the term "executive management" has been changed to "management with executive responsibility," to harmonize with ISO 9001:1994.

14 Several comments in response to the proposed definition of "manufacturer" stated that refurbishers and servicers should be added to the definition of a "manufacturer." Other comments requested deletion of contract sterilizers, specification developers, repackagers, relabelers, and initial distributors from the definition.

FDA agrees with the comments that refurbishers and servicers should be included in the definition of a "manufacturer" to be consistent with the intent and

requirements of the Quality System regulation, since refurbishers and servicers may have a significant impact on the safety and effectiveness of medical devices. Further, such persons are in fact manufacturing and/or processing medical devices.

FDA's Compliance Policy Guide, CPG 7124.28, contains the agency's current policy regarding the provisions of the act and regulations with which persons who recondition or rebuild used devices are expected to comply. This CPG is in the process of being revised in light of FDA's current thinking. All persons who are refurbishers will now be expected to comply with the applicable Quality System regulation requirements. A definition of "refurbisher" has been added in section 820.3(y).

Servicers will be required to follow the requirements set forth in section 820.200 on "Servicing."

FDA disagrees with the comments that contract sterilizers, specification developers, repackagers, relabelers, and initial distributors should be deleted from the definition, primarily because all such persons may have a significant effect on the safety and effectiveness of a device and on the public health. All of these persons must be inspected to ensure that they are complying with the applicable provisions. For example, initial distributors are required to maintain complaint files under the Medical Device Reporting (MDR) regulation, and also may service, or otherwise manufacture, devices they distribute. Similarly, a specification developer initiates the design requirements for a device that is manufactured by a second party for subsequent commercial distribution. Such developer is subject to design controls.

15 One comment stated that the phrase "processes a finished device" should be explained in the definition of manufacturer.

The phrase "processes a finished device" applies to a finished device after distribution. Processing a device includes, among other things, repairing, servicing, and reconditioning the device. Again, this phrase has been part of the CGMP regulation definition for 15 years.

16 A number of comments on the definition of "manufacturing material," and on other parts of the proposal containing requirements for "manufacturing material," stated that while the control of manufacturing material is important, it need not be as extensive as required throughout the regulation.

FDA agrees that, depending on the manufacturing material and the device, the degree of control necessary will vary. FDA believes that manufacturing materials must be assessed, found acceptable for use, and controlled. Therefore, the regulation requires manufacturers to assess, assure acceptability of, and control manufacturing materials to the degree necessary to meet the specified requirements. The agency notes that international standards such as ISO 8402:1994 include manufacturing material in their definition of "product," to which all requirements apply, and notes that FDA has added the same definition in section 820.3(s) in its effort toward harmonization.

17 Other comments stated that the meaning of the phrase "or other byproducts of the manufacturing process" is unclear, and should be deleted.

The term "or other byproducts of the manufacturing process" means those materials or substances that naturally occur as a part of the manufacturing process which are intended to be removed or reduced in the finished device. For example, some components, such as natural rubber latex, contain allergenic proteins that should be reduced or removed. The definition has been modified to include "naturally occurring substances" to clarify the intent. Further, in a response to a comment, "ethylene oxide" was removed as a specific example of "sterilant residues," as it is unnecessary.

18 The comments received on the definition for "nonconforming" conveyed a general sense that the definition was confusing, with various comments suggesting that different parts of the definition be should deleted and one suggesting that the definition be deleted altogether.

In response to these comments, the definition of "nonconforming" has been deleted. However, the definition from ISO 8402:1994 for "nonconformity" was added to ensure that the requirements in the regulation, especially those in sections 820.90, "Nonconforming product" and 820.100, "Corrective and preventive action," are understood. FDA emphasizes that a "nonconformity" may not always rise to the level of a product defect or failure, but a product defect or failure will always constitute a nonconformity.

19 Several comments requested various revisions to the definition of "production" to make it more clear and one thought that it was a common term and should be deleted.

In response, FDA has deleted the definition for "production" because it should be commonly understood.

As noted in response to comments on the definition of manufacturing material, FDA has added a definition of "product," to conform to the definition in ISO 8402:1994 and to avoid the necessity of repeating the individual terms throughout the regulation. Whenever a requirement is not applicable to any one type of product, the regulation specifically states the product(s) to which the requirement is applicable.

20 A few comments stated that the definition of "quality" should be changed to be identical to ISO 8402. Others stated that the terminology adopted from ISO 8402, "that bears on," is too broad and could cover every potential and imaginable factor. Still others wanted to add the phrase, "as defined by the manufacturer" to the end of the sentence.

FDA disagrees with the comments and believes that the definition is closely harmonized to that in ISO 8402. FDA believes that the definition appropriately defines quality in the context of a medical device, and does not believe that the phrase from ISO 8402, "stated and implied needs," has a different meaning than the phrase "fitness for use, including safety and performance" in the context of the Quality System regulation. Further, "quality" is not just those aspects "defined by the manufacturer," but is also those defined by customer need and expectation.

21 Many comments received on the "quality audit" definition suggested that the definition should not state that it is an examination of the "entire" quality system because that would require that every audit include the "entire" quality system.
FDA agrees that while the quality audit is an audit of the "entire" quality system, audits may be conducted in phases, with some areas requiring more frequent audits than other areas, and that each audit need not review the whole system. Internal quality audits should be scheduled consistent with, among other things, the importance of the activity, the difficulty of the activity to perform, and the problems found. Audits must include a review and evaluation of all parts of a quality system, including its procedures, records, and processes, among other things. To avoid any misunderstanding, the word "entire" before quality system has been deleted.

FDA emphasizes that if applied properly, internal quality audits can prevent major problems from developing and provide a foundation for the management review required by section 820.20(c), "Management review."

22 Other comments on "quality audit" stated that it is unclear what is meant by the last sentence of the definition, namely, that "'[q]uality audit' is different from...other quality system activities required by or under this part."

In response, FDA has deleted the last sentence. The purpose of the sentence was to clarify that the internal audit requirement is different from, and in addition to, the requirements for establishing quality assurance procedures and recording results. On occasion, manufacturers have attempted to prevent FDA investigators from reviewing such quality assurance procedures and results (for example, trend analysis results) by stating that they are part of the internal quality audit report and not subject to review during a GMP inspection. FDA disagrees with this position. To clarify which records are exempt from routine FDA inspection, FDA has added section 820.180(c).

23 One comment said that the word "executive" should be deleted from the definition of "quality policy" because quality policy should be supported by all personnel, not just those in executive management.

FDA agrees that all company personnel must follow the quality policy, however, the definition is intended to make clear that the quality policy must be established by top management and has therefore been retained. The term "executive management" has been modified to "management with executive responsibility" to be consistent with the revised ISO 9001:1994.

24 A few comments suggested using the definition of "quality systems" from ISO 8402 and 9001. Other comments on the definition of "quality system" said that the term "quality management" should be defined.

FDA agrees in part with the comments. The term "specifications" has been deleted to harmonize the definition with ISO 8402:1994. FDA does not agree that the term "quality management" must be defined. A definition can be found in ISO 8402:1994 that is consistent with FDA's use of the term.

25 Several comments on the definition of "record" were received. Some thought the term was too broad, giving FDA access to all documents and exceeding FDA's inspection authority. Another comment requested clarification on what an "automated document" was compared to an "electronic document."

FDA has modified the term "automated" in the definition in favor of the term "electronic," to be consistent with the current terminology. FDA disagrees with the other comments. The definition is intended to clarify that "records" may include more than the traditional hardcopy procedures and SOPs, for example, plans and notes. The definition is not intended to, and does not, subject a manufacturer's records to FDA inspection where such records are unrelated to the requirements of the regulation.

26 Several comments on the definition of "reprocessing" requested clarification between that term and "refurbishing." Several other comments on the definition of "reprocessing" stated that FDA should clarify that "reprocessing" was an activity performed before a device is distributed.

In response, FDA has revised the definition of "reprocessing" to specify that reprocessing is action taken before distribution. FDA has also added a definition for "refurbisher." The definition proposed is similar to the definition from the working draft revision of ISO/DIS 13485 "Quality Systems - Medical Devices - Supplementary Requirements to ISO 9001." "Refurbishing" is action taken on a device "which has been previously distributed and has reached its established end-of-life or is considered to be nonrepairable," irrespective of whether the person performing the activity takes ownership of the device or the device is resold. Refurbishers are manufacturers.

27 A few comments stated that including the term "maintenance" in the definition of "servicing" implies that preventative maintenance would be subject to the regulation. Other comments said that it may not be desirable to return old devices or devices that have received field modifications to the original specifications. Therefore, the comments suggested deleting the last part of the definition that

states that "servicing" is returning a device to its specifications.

FDA meant for maintenance to be covered by the definition and has included the term "maintenance" in the servicing definition to make that clear. "Maintenance" is subject to the requirements in section 820.200, "Servicing." In response to the comments regarding old or modified devices, FDA has modified the definition to say that servicing is performed "after distribution for the purposes of returning it to its safety and performance specifications so it will meet its original intended use, prior to the device's established end-of-life." Servicing may take place on a refurbished device as well.

28 Several comments were received on the definition of "special process," many asking for clarification or adoption of the ISO definition, some stating that it is impossible to 100 percent verify any process.

FDA has deleted the definition because the term "special process" is no longer used in ISO 9001:1994, except in a note. FDA has, however, modified the requirements of the regulation to reflect that, in many cases, testing and inspecting alone may be insufficient to prove the adequacy of a process. One of the principles on which the Quality Systems regulation is established is that all processes require some degree of qualification, verification, or validation, and manufacturers should not rely solely on inspection and testing to ensure processes are adequate for their intended use.

29 Several comments on the definition of "specification" suggested that the term should not apply to quality system requirements. One comment noted that the definition in ISO 9001 pertains to requirements, not only documents.

In response, FDA has amended the definition to make clear that it applies to the requirements for a product, process, service, or other activity. The reference to the quality system has been deleted. FDA notes, however, that ISO 9001 does not contain a definition for "specification," but uses the definition in ISO 8402.

30 Many comments were received on the definitions of "validation" and "verification." Almost all stated that the two definitions overlapped and that there was a need to rewrite the definitions to prevent confusion.

FDA agrees with the comments and has rewritten the two definitions to better reflect the agency's intent. "Validation" is intended to be a process undertaken to establish that the manufacturer's processes will consistently produce a desired result or a product which meets its predetermined specification. The revised definition follows from FDA's "Guideline on General Principles of Process Validation" and is consistent with the definition contained in ISO 8402:1994. The requirements for design validation are contained in section 820.30, "Design controls."

The definition of "verification" now more closely parallels the definition in ISO 8402:1994. "Verification" is not related to determining whether future requirements will be met, but whether requirements for a particular device or activity at hand have been met.

iii. Quality system

1 Several comments suggested that the requirement should be more general, in that the more specific requirement that devices be safe and effective is covered elsewhere in the regulation. The comments recommended that the quality system requirements be harmonized with international standards and focus on requiring that a system be established that is appropriate to the specific device and that meets the requirements of the regulation.

FDA agrees in part with the comments and has modified the language as generally suggested by several comments to require that the quality system be "appropriate to the specific medical device manufactured and meet the requirements of this

part." This is the requirement of the current device CGMP regulation; however, the Quality System regulation now includes requirements related to design, purchasing, and servicing controls. As proposed, the provision was redundant with section 820.1, which states that the intent of the Quality System regulation is to ensure that finished devices will be safe and effective.

The specific requirements that effective quality system instructions and procedures be established and effectively maintained are retained, however. As previously noted, the quality system regulation is premised on the theory that the development, implementation, and maintenance of procedures designed to carry out the specific requirements will ensure the safety and effectiveness of devices. Thus, the broad requirements in section 820.5 are in a sense the foundation on which the specific requirements are built. Therefore, although several comments suggested that the sections 820.5(a) and (b) should be deleted because other sections of the regulation contain a specific requirement for procedures, FDA has retained the requirements.

2 In addition, although comments stated that the terms "effective" and "effectively" should be defined, FDA does not believe that the terms require a definition. Instructions and procedures must be defined, documented, implemented, and maintained in such a way that the requirements of this part are met. If they are, they will be "effective."

<A NAME="pSubpart B">B. Quality System Requirements (Subpart B)</A>

i. Management responsibility

1 Several comments on section 820.20(a), "Quality policy," related to the use of the term "executive management." A few comments stated that quality system development and implementation is the responsibility of the chief executive officer, but how he or she chooses to discharge the responsibility should be left to the discretion of the manufacturer. Other comments stated that the requirement that executive management ensure that the quality policy is understood is impossible and should be deleted or rewritten.

FDA agrees in part with the comments. In response to the comments, FDA has deleted the term "executive management" and replaced it with "management with executive responsibility," which is consistent with ISO 9001:1994. Management with executive responsibility is that level of management that has the authority to establish and make changes to the company quality policy. The establishment of quality objectives, the translation of such objectives into actual methods and procedures, and the implementation of the quality system may be delegated. The regulation does not prohibit the delegation. However, it is the responsibility of the highest level of management to establish the quality policy and to ensure that it is followed.

For this reason, FDA disagrees that the requirement that management ensure that the quality policy is understood should be deleted. It is without question management's responsibility to undertake appropriate actions to ensure that employees understand management's policies and objectives. Understanding is a learning process achieved through training and reinforcement. Management reinforces understanding of policies and objectives by demonstrating a commitment to the quality system, visibly and actively on a continuous basis. Such commitment can be demonstrated by providing adequate resources and training to support quality system development and implementation. In the interest of harmonization, the regulation has been amended to be very similar to ISO 9001:1994.

2 Two comments stated that the words "adequate" and "sufficient" should be deleted from section 820.20(b), "Organization," as they are subjective and too difficult to define. One comment thought that the general requirements in the subsections are addressed by section 820.25, "Personnel."

FDA agrees that the requirement for "sufficient personnel" is covered in sections

820.20(b)(2), "Resources" and 820.25, "Personnel," both of which require each manufacturer to employ sufficient personnel with the training and experience necessary to carry out their assigned activities properly. The phrase is therefore deleted. However, FDA has retained the requirement for establishing an "adequate organizational structure" to ensure compliance with the regulation because such an organizational structure is fundamental to a manufacturer's ability to produce safe and effective devices. Further, the agency does not believe that the term is ambiguous. The organizational structure established will be determined in part by the type of device produced, the manufacturer's organizational goals, and the expectations and needs of customers. What may be an "adequate" organizational structure for manufacturing a relatively simple device, may not be "adequate" for the production of defibrillators.

3 A number of comments on section 820.20(b)(1), "Responsibility and authority," subsections (i) through (v), objected to the section, stating that it was too detailed and confusing, and that the wording was redundant with other sections of the proposal.

FDA agrees generally with the comments in that the subsections merely set forth examples of situations in which independence and authority are important, but the broad requirement is for the necessary independence and authority to be provided as appropriate to every function affecting quality. Therefore, the examples provided in (i) through (v) are deleted. FDA emphasizes that it is crucial to the success of the quality system for the manufacturer to ensure that responsibility, authority, and organizational freedom (or independence) is provided to those who initiate action to prevent nonconformities, identify and document quality problems, initiate, recommend, provide, and verify solutions to quality problems, and direct or control further processing, delivery, or installation of nonconforming product.

4 Several comments on section 820.20(b)(2), "Verification resources and personnel" stated that requiring "adequately" trained personnel was subjective and interpretive and that the section was not consistent with ISO 9001.

FDA agrees that the section is not consistent with ISO 9001, and has adopted the language used in ISO 9001:1994, section 4.1.2.2, "Resources." The provision is now more appropriately a broad requirement that the manufacturer provide adequate resources for the quality system, and is not restricted to the verification function. FDA acknowledges that section 820.25(a), "Personnel" requires that sufficiently trained personnel be employed. However, this section on "Resources" emphasizes that all resource needs must be provided for, including monetary as well as personnel resources. In contrast, section 820.25(a) addresses specific education, background, training, and experience requirements for such personnel.

5 Comments on section 820.20(b)(3), "Management representative" stated that the management representative should not be limited to "executive" management. A few comments stated that the appointment should be documented.

The agency agrees that the responsibility need not be assigned to "executive" management and has modified the requirement to allow management with executive responsibility to appoint a member of management. When a member of management is appointed to this function, potential conflicts of interest should be examined to ensure that the effectiveness of the quality system is not compromised. In addition, in response to many comments, the requirement was amended to make clear that the appointment of this person must be documented, moving the requirement up from subsection (ii). The amended language is consistent with ISO 9001:1994.

6 A few comments stated that the improvement of the quality system is not a specific requirement under the Food, Drug, and Cosmetic Act and the reference to such improvement in subsection 820.20(b)(3)(ii) should, therefore, be deleted.

FDA agrees in part with the comments and has deleted the requirement that the

person appointed under this section provide information for improving the quality system. The provision implied that the manufacturer must go beyond the requirements of the regulation. FDA notes, however, that information collected in complying with this section and section 820.100, "Corrective and preventive action" should be used not only for detecting deficiencies and for subsequent correction of the deficiencies, but to continuously improve the device and quality system.

Further, FDA has amended this section to change "executive management" to "management with executive responsibility" for consistency with the definition.

7 Many comments stated that the report required by section 820.20(c), "Management review" should not be subject to FDA review, due to the same liability and self-incrimination concerns related to the internal audit.

FDA agrees in part with the comments. The proposed regulation did not state FDA's intentions with respect to inspectional review of the results of the required management review. After careful consideration of the comments, FDA agrees that it will not request to inspect and copy the reports required by the section when conducting routine inspections to determine compliance with this part. FDA believes that refraining from routinely reviewing these records may help ensure that the audits are complete and candid, and of maximum use to the manufacturer. FDA may require that management with executive responsibility certify in writing that the manufacturer has complied with the requirements of section 820.20(c), however. FDA will review the written procedures required by section 820.20(c), as well as all other records required under section 820.20.

8 A few comments stated that the management review should not be dictated by established review procedures because management level employees should be fully capable of reviewing documents without a written procedure.

As noted above, FDA has retained the requirement for establishing procedures to conduct the required quality system review in section 820.20(c). FDA believes that a manufacturer can establish procedures flexible enough for management to vary the way in which a review is conducted, as appropriate. Procedures should require that the review be conducted at appropriate intervals and should be designed to ensure that all parts of the quality system are adequately reviewed. A manufacturer may, of course, develop procedures that permit review of different areas at different times, so long as such review is sufficient to carry out the objectives of this section. If there are known problems, for example, a "sufficient frequency" may be fairly frequent. Further, since FDA will not be reviewing the results of such reviews, FDA must be assured that this function will occur in a consistent manner.

9 A few comments stated that section 820.20(c) should be deleted because it duplicates the quality audit required by section 820.22.

FDA disagrees that section 820.20(c) duplicates the requirements in section 820.22. The purpose of the management reviews required by section 820.20(c) is to determine if the manufacturer's quality policy and quality objectives are being met, and to ensure the continued suitability and effectiveness of the quality system. An evaluation of the findings of internal and supplier audits should be included in the section 820.20(c) evaluation. The management review may include a review of the following: the organizational structure, including the adequacy of staffing and resources; the achieved quality of the finished device in relation to the quality objectives; combined information based on purchaser feedback, internal feedback (such as results of internal audits), process performance, product (including servicing) performance, among other things; and internal audit results and corrective and preventive actions taken. Management should also review periodically the appropriateness of the review frequency, based on the findings of previous reviews. The quality system review process in section 820.20(c), and the

reasons for the review, should be understood by the organization.

The requirements under section 820.22, "Quality audit" are for an internal audit and review of the quality system to verify compliance with the Quality System regulation. The review and evaluations under section 820.22 are very specific. During the internal quality audit, the manufacturer should review all procedures to ensure adequacy and compliance with the regulation, and determine whether the procedures are being effectively implemented at all times. In contrast, as noted above, the management review under section 820.20(c) is a broader review of the organization as a whole to ensure that the quality policy is implemented and the quality objectives are met.

ii. Quality Audit

1 A few comments suggested that FDA delete the requirement that persons conducting the audit be "appropriately trained" from the second sentence of 820.22(a) because it is subjective and not consistent with ISO 9001.

FDA has deleted the requirement from this section because section 820.25, "Personnel" requires that such individuals be appropriately trained. Further, FDA has attempted to better harmonize with ISO 9001, which does not explicitly state personnel qualifications in each provision. Similarly, in response to general comments suggesting better harmonization, FDA has added the requirement that the audit "determine the effectiveness of the quality system," as required by ISO 9001:1994. This requirement underscores that the quality audit must not only determine whether the manufacturer's requirements are being carried out, but whether the requirements themselves are adequate.

2 Some comments stated that requiring "individuals who do not have direct responsibility for the matters being audited" to conduct the audits is impractical and burdensome, particularly for small manufacturers.

FDA disagrees. Both small and large manufacturers have been subject to the identical requirement since 1978 and FDA knows of no hardship, on small or large manufacturers, as a result. A small manufacturer who believes that it can ensure that the audit will be appropriately conducted without independence may apply for a variance or an exemption, pursuant to section 820.1(e). However, small manufacturers must generally establish independence, even if it means hiring outside auditors, because the failure to have an independent auditor could result in ineffective audit.

Manufacturers must realize that conducting effective quality audits is crucial. Without the feedback provided by the quality audit and other information sources, such as complaints and service records, manufacturers operate in an open loop system with no assurance that the process used to design and produce devices is operating in a state of control. ISO 9001:1994 has the same requirement for independence from the activity being audited.

3 Several comments claimed that the last sentence in section 820.22(a), requiring that follow-up corrective action be documented in the audit report, made no sense. The comments said that corrective action would be the subject of a follow-up report.

It was the agency's intent that the provision require that where corrective action was necessary, it would be taken and documented in a reaudit report. The provision has been rewritten to make that clear. The new section should also clarify that a reaudit is not always required, but where it is indicated, it must be conducted. The report should verify that such corrective action was implemented and effective. Because FDA does not review these reports, the date on which the audit and reaudit was performed must be documented, and will be subject to FDA review. The revised reaudit provision is consistent with ISO 9001:1994.

4 Many comments were received on section 820.22(b) regarding the reports exempt from FDA review. Most of the comments objected to FDA reviewing evaluations of suppliers. FDA has decided not to review such evaluations at this time and will revisit this decision after the agency gains sufficient experience with the new requirement to determine its effectiveness. A thorough response to the comments is found with the agency's response to other comments received on section 820.50, "Purchasing controls." FDA has moved the section regarding which reports the agency will refrain from reviewing from section 820.22(b) to new section 820.180(c), "Exemptions," under the related records requirements. FDA believes this organization is easier to follow.

iii. Personnel

1 A few comments stated that the requirement in section 820.25, "Personnel" for the manufacturer to employ "sufficient" personnel should be deleted because whether there are "sufficient" personnel is a subjective determination, and it is unnecessary to require it since the manufacturer will know how best to staff the organization. A few other comments stated that the provision should not base the personnel requirements on ensuring that the requirements of the regulation are "correctly" performed because no manufacturer can ensure that all activities are performed correctly.

FDA disagrees with the suggestions that these terms be deleted. Whether "sufficient" personnel are employed will be determined by the requirements of the quality system, which must be designed to ensure that the requirements of the regulation are properly implemented. In making staffing decisions, a manufacturer must ensure that persons assigned to particular functions are properly equipped, and possess the necessary education, background, training, and experience to perform their function correctly. That mistakes may occur is beside the point. Further, FDA agrees that the manufacturer must determine for itself what constitutes "sufficient" personnel with proper training, among other things, in the first instance. However, if the manufacturer does not employ sufficient personnel, or personnel with the necessary qualifications to carry out their functions, the manufacturer will be in violation of the regulation. FDA has often found that the failure to comply with this requirement leads to other significant regulatory violations.

2 In section 820.25(b), "Training," FDA deleted the requirement that employees be trained "by qualified individuals" because section 820.25(a) requires this. FDA retained the rest of section 820.25(b), although several comments suggested deleting the specific requirements in the last two sentences in favor of a broad, general requirement that personnel be trained. FDA believes that it is imperative that training cover the consequences of improper performance so that personnel will be apprised of defects that they should look for, as well as be aware of the effect their actions can have on the safety and effectiveness of the device. In addition, FDA also disagrees with comments that suggested that only "personnel affecting quality" should be required to be adequately trained. In order for the full quality system to function as intended, all personnel should be properly trained. Each function in the manufacture of a medical device must be viewed as integral to all other functions.

3 Many comments objected to the proposed requirements of 820.25(c), "Consultants," stating that requiring a manufacturer to chose consultants that have sufficient qualifications, and to keep records subject to FDA review of all consultants used, along with a copy of their curriculum vitae and list of previous jobs, would unreasonably interfere with the manufacturer's business activities and restrict the right of a manufacturer to hire consultants on any basis it chooses. Other comments said that a manufacturer's employment of a consultant has the same potential impact on the safety and effectiveness of medical devices as employment of any other contractor for services, and that consultants should, therefore, be covered by section 820.50, "Purchasing controls."

FDA agrees in part with these comments. Although employing a consultant is a business decision, where a manufacturer hires consultants that do not have appropriate credentials, and manufacturing decisions are made based on erroneous or ill conceived advice, the public suffers. Of course, the manufacturer is still ultimately responsible for following the CGMP requirements, and will bear the consequences of a failure to comply. And, FDA notes that the use of unqualified consultants has led to regulatory action for the failure to comply with the CGMP regulation. But this is little consolation to those who may be harmed by the devices. Thus, because of the significant impact a consultant can have on the safety and effectiveness of a device, FDA believes that some degree of control is required in the regulation.

The requirements are revised somewhat in response to comments, however, to reflect that it is not FDA's goal to dictate whom a manufacturer may use as a consultant, but to require that a manufacturer determine what it needs to adequately carry out the requirements of the regulation and to assess whether the consultant can adequately meet those needs. The requirements related to consultants have been added in section 820.50, "Purchasing controls" because a consultant is a supplier of a service.

<A NAME="pSubpart C">C. Design Controls (Subpart C)</A>

1 Many comments were submitted in response to the addition of design control requirements in general, many questioning how this new requirement would be implemented and enforced. For instance, several comments stated that the design control requirements do not reflect how medical devices are actually developed, because the concept of a design rarely originates with the manufacturer, who may not become involved until relatively late in the design evolution. Others expressed concern that FDA investigators will second-guess design issues in which they are not educated or trained, and the opinion that the investigator should not debate whether a medical device design is "safe and effective."

FDA disagrees. The design control requirements are not intended to apply to the development of concepts and feasibility studies. However, once it is decided that a design will be developed, a plan must be developed for establishing the adequacy of the design requirements and ensuring that the design that will eventually be released to production meets the approved requirements.

Those who design medical devices must be aware of the design control requirements in the regulation and comply with the applicable requirements of the regulation. Unsafe and ineffective devices are often the result of informal development that does not ensure the proper establishment of design requirements and does not provide for proper assessment of the device requirements, which are necessary to develop a medical device with the proper level of safety and effectiveness for the intended use of the device and needs of the user.

FDA investigators will not inspect a device under the design control requirements to determine whether the design was appropriate, or "safe and effective," but will evaluate the process, the methods, and the procedures that a manufacturer has established to implement the requirements for design controls. If the investigator finds during an inspection that distributed devices are unsafe or ineffective, the investigator has an obligation to report the observations to the Center for Devices and Radiological Health (CDRH).

2 Several comments expressed concern that the application of design controls would severely restrict the creativity and innovation of the design process and suggested that FDA should not begin application of the regulation too early in the design development process.

FDA disagrees with the comments. It is not the intent of FDA to interfere with creativity and innovation, and it is not the intent of FDA to apply the design control requirements to the research phase. Instead, the regulation establishes requirements for the establishment of procedures to ensure that whatever design is ultimately transferred to production is in fact a design that will translate into a

device that properly performs according to its intended use and meets the user's needs.

To assist FDA in applying the regulation, manufacturers should document the flow of the design process so that it is clear to the FDA investigator where research ends and development of the design begins.

3 A few comments stated that design controls should not be retroactive and that ongoing design development should be exempted.

FDA agrees in part. FDA did not intend the design requirements to be retroactive, and section 820.30, "Design controls" will not require the manufacturer to apply such requirements to already distributed devices. When the regulation becomes effective, it will apply to designs that are within the design and development phase, and manufacturers will be expected to have the design and development plan established. The manufacturer should identify at what stage that design is in for such devices, and will be expected to comply with the established design and development plan and the applicable parts of section 820.30 from that point forward to completion. It will not be mandatory for designs to be recycled through previous phases, however, that have been completed.

However, when changes are made to new or existing designs, the design controls of section 820.30 must be followed to ensure that the changes are appropriate, and that the device will continue to perform as intended. FDA notes that the current device CGMP regulation contains requirements for specification controls and controls for specification or design changes under section 820.100(a).

4 One comment asked how the proposed design controls would apply to Investigational Device Exemption (IDE) devices, since devices under an approved IDE are now exempt from the CGMP regulation.

Devices being evaluated under an IDE were exempted from the current device CGMP regulation because it was believed that it was not reasonable to expect manufacturers to set up full scale manufacturing facilities and procedures to manufacture devices that may never be approved for commercial development and distribution. However, manufacturers conducting IDE studies were required to manufacture the devices used in the studies under a state of control.

With respect to the new regulation, FDA believes that it is reasonable to expect manufacturers who design medical devices to develop the designs complying with design control requirements and that imposing such requirements is necessary to adequately protect the public from potentially dangerous devices. The design control requirements are basic controls needed to ensure that the device being investigated will be the same or similar to the device later produced for commercial distribution. FDA intends to amend the IDE regulation to clearly state that IDE devices are not exempt from section 820.30, "Design controls" in the Quality System regulation.

5 One comment recommended that because design controls are a major addition to the regulation, the effectiveness date for design controls should be delayed to 18 months after publication of the final regulation.

FDA has stated its intentions to add design controls to the CGMP requirements for over six years. In 1989, CDRH published recommendations for preproduction quality assurance entitled "Preproduction Quality Assurance Planning: Recommendations for Medical Device Manufacturers." In November of 1990, FDA published suggested design control requirements in the document "Suggested Changes to the Medical Device Good Manufacturing Practices Regulation Information Document." Hence, the agency believes that the device industry has had ample notice and time to prepare and implement design controls.

6 A few comments objected to FDA requiring design controls for any Class I devices.

FDA believes that, for the Class I devices listed, design controls are necessary and has retained the requirements. Those relatively few devices, while Class I, require close control of the design process to ensure that the devices perform as intended, given the serious consequences that could occur if their design was flawed and the devices were to fail to meet their intended use. In fact, some of the devices included on the list have experienced failures due to design related problems that have resulted in health hazards, injuries, or death. Further, verification, or even validation, cannot provide the assurance of proper design for some devices, such as those containing software. FDA notes that design controls for computer software is believed to be necessary for many industries, even those not concerned with safety. Thus, all automated devices must be developed under the design control requirements.

7 A couple of comments suggested that FDA lacked the authority to establish the design control requirements.

FDA disagrees. The plain language of the statute and the legislative history make clear that FDA has the authority to impose those controls necessary to ensure proper device design. SMDA gave FDA explicit authority to include design validation controls, to "include" a process to assess the performance of the device. Section 520(f)(1)(A) of the act (21 U.S.C. 360j(f)(1)(A)). This language thus makes clear that FDA is not limited to one process control related to design. Further, in adding the CGMP design provision, Congress noted that while it was aware that FDA contended that it had the authority to require design validation without explicit language to that effect, there was some question whether the authority would permit the agency to promulgate a "comprehensive device design validation regulation." H.R. Rep. No. 808, 101st Cong., 2d Sess. 23 (emphasis added). Congress stated that the amendment to the statute was necessary because almost half of all device recalls over a five year period were "related to a problem with product design." Id.

In addition, the purpose of the CGMP requirements is to "assure that [a] device will be safe and effective and otherwise in compliance with [the] Act)." Section 520(f)(1)(A) of the act (21 U.S.C. 360j(f)(1)(A)). Thus, to carry out the objectives of the act, FDA believes that the design controls required by the regulation are those which are necessary to ensure a properly designed device, capable of performing as intended by the manufacturer and as needed by the user. There is a thorough discussion on the evolution of and need for the design controls in the preamble to the November 23, 1993, proposal (58 FR 61592).

8 Several comments stated that FDA has underestimated the complexity of a design project in requiring that the plans identify "persons responsible for each activity" in section 820.30(b).

FDA agrees with the comments and has revised section 820.30(b) to require the plan to describe or reference design activities and define responsibility for implementing the activities, rather than requiring that the plan identify each person responsible for carrying out each activity. In making this change, FDA notes that section 820.20(b)(1) requires manufacturers to establish the appropriate responsibility for activities affecting quality, and emphasizes that the assignment of specific responsibility is important to the success of the design control program and to achieve compliance with the regulation. The requirements under section 820.30(b) are very similar to the requirements in ISO 9001:1994, section 4.4.2 and 4.4.3.

9 A few comments stated that the requirement for the design and development plan to describe "any interaction between or among different organizational and

technical groups" should be deleted because it is overly broad, unnecessary, and burdensome. One comment said that the communication expected between these groups should be clarified.

In response, FDA has amended the requirement to provide that interfaces with different groups or activities shall be included in the plan. Many organization functions, both inside and outside the design organization, may contribute to the design process. For example, interfaces with marketing, purchasing, regulatory affairs, manufacturing, service groups, and information systems, among other groups, may be necessary during the design development phase. To function effectively, the design plan must establish the roles of these groups in the design process and describe the information that should be received and transmitted.

10 One comment stated that the requirement that manufacturers establish a design plan completely ignores the creative and dynamic process of designing by requiring a plan to have complete design and testing criteria established, with specifications, before the design process is started.

FDA disagrees with the comment. Section 820.30(b) does not require manufacturers to complete design and testing criteria before the design process begins. This section has been revised to state that "plans shall be reviewed, updated, and approved as design and development evolves," indicating that changes to the design plan are expected. A design plan typically includes at least proposed quality practices, assessment methodology, record-keeping and documentation requirements, and resources, as well as a sequence of events relative to a particular design or design category. These may be modified and refined as the design evolves. However, the design process can become a lengthy and costly process if the design activity is not properly defined and planned. The more specifically the activities are defined up front, the less need there will be for changes as the design evolves.

11 Several comments stated that the requirement of ISO 9001 that "incomplete, ambiguous or conflicting requirements shall be resolved with those responsible for imposing these requirements" should be added to section 820.30(c), "Design input," because it is important that the regulations identify the method of resolving conflicting information.

FDA agrees in part with the comments, in that it is important that incomplete, ambiguous, or conflicting requirements be resolved with those responsible for imposing these requirements. However, FDA notes that this must be done to "ensure that the design requirements are appropriate and address the intended use of the device," as required under section 820.30(c). Therefore, this requirement is inherent in the requirements of section 820.30(c) and need not be added to the language of the regulation.

12 One comment stated that the language contained in section 820.30(c) should more closely match that of ISO 9001. Many other comments stated that the provision should not require the input requirements to "completely" address the intended use of the device because inputs could never "completely" address the intended use.

FDA agrees with the harmonization comment and has revised the language to incorporate the requirement of clause 4.4.4, "Design input" of ISO 9001:1994. FDA does not believe that it is necessary to have identical language to harmonize quality system requirements. ISO 9001:1994, section 4.4.1, "General" requires that the manufacturer "establish and maintain documented procedures to control and verify the design of the product in order to ensure that the specified requirements are met." FDA's regulation, under section 820.30(a), imposes the same requirements.

Regarding the comments on the requirement that input requirements completely address the intended use of the device, FDA recognizes that the provision could be interpreted to impose a burden that may not always be possible to meet and has

deleted the word "completely." FDA did not intend the provision to suggest that a manufacturer must foresee events that are impossible to have imagined.

FDA emphasizes, however, that the section requires the manufacturer to ensure that the design input requirements are appropriate to ensure that the device will perform to meet its intended use and the needs of the user. In doing this, the manufacturer must assess and set the proper level of safety and effectiveness that is commensurate with the intended use of the device. This process involves defining the performance characteristics, safety and reliability requirements, environmental requirements and limitations, physical characteristics, applicable standards and regulatory requirements, and packaging, and labeling requirements, among other things, and refining the design requirements as verification results are established. For example, when establishing the physical characteristics of a device, the manufacturer should conduct appropriate human factors studies, analyses, and tests from the early stages until the point of interface with the user and patient is fixed. The procedures used (for instance, task/function analyses, mockup reviews, user tests, among others) should ensure that the characteristics of the user population and operating environment are considered throughout the process.

13 A few comments stated that the requirement under section 820.30(c) that "design input shall be reviewed and approved by a designated qualified individual" should be deleted as it implies that one person must be designated to review and approve a design, and that there may not be one person that is qualified to assess all of the design input requirements. Addressing the same point, several comments suggested that the provision be revised to allow for more than one person to review and approve the design. One comment said that the FDA requirement appears to be at odds with the team approach.

FDA agrees with the concern expressed by the comments and has modified the requirement to allow more than one individual to review and approve the design input. FDA endorses the team approach and believes that designs should be reviewed and evaluated by all disciplines necessary to ensure the design input requirements are appropriate.

14 Two comments stated that section 820.30(c) should be reworded to focus on systems for assuring adequate design input, not on the input itself.

FDA agrees that procedures for ensuring appropriate design controls are of the utmost importance and has modified the section to clarify that the manufacturer must establish and maintain procedures to ensure that the design requirements are properly addressed. FDA made this change to the other subsections as well, but notes that section (a), "General" requires the manufacturer to establish and maintain procedures to verify the design of the device in order to ensure that specified design requirements are met. The sections that follow set forth some of the specific requirements for which procedures must be established. It should be emphasized that the input itself must also be appropriate; the requirement is for the procedures to be defined, documented, and implemented. Thus, if the input requirements related to a device fail to address the intended use of the device, for example, the manufacturer has failed to comply with the provision.

One additional comment on this section said that the design input requirements should include not only the device's intended use and needs of the user, but the environmental limits of where it will be used.

FDA agrees with the comment, but believes that identifying and establishing the environmental limits for safe and effective device operation is inherent in the requirements for ensuring that a device is appropriate for its intended use. A device cannot meet its intended use requirements if it is adversely affected by the environment. Some factors that must be considered when establishing inputs include, as applicable, a determination of energy (for example, electrical, heat, and

electromagnetic fields), biological affects (for example, toxicity and bioincompatibility) and environmental affects (for example, electromagnetic interference and electrostatic discharge).

15 Several comments stated that section 820.30(f), "Design output," should be rewritten or deleted because many of the requirements were already stated in sections 820.30(d), "Design verification" and (e), "Design review" and, if retained, should be reordered similar to ISO 9001.

FDA agrees in part with the comments and has rewritten the requirements of design output to be consistent with ISO 9001:1994 section 4.4.5, "Design output" and reordered the sections to be consistent with ISO 9001:1994 ordering. FDA retained the provision, however, because it does not agree that the section is redundant with the sections on design verification and validation and review. Design output are the design specifications which should meet design input requirements, as confirmed during design verification and validation and ensured during design review. The output includes the device, its packaging and labeling, associated specifications and drawings, and production and quality assurance specifications and procedures. These sections are not redundant, but dependent on each other.

16 One small manufacturer commented that the problems that section 820.30(e), "Design review" requirements are meant to reveal involve coordination, cooperation, or communication difficulties among the members of an organization and that these difficulties do not exist in a small company. Therefore, the comment stated that the design review requirements should not apply to small manufacturers.

The purpose of conducting design reviews during the design phase is to ensure that the design satisfies the design input requirements for the intended use of the device and the needs of the user. Design review includes the review of design verification activities to determine whether the design outputs meet functional and operational requirements, the design is compatible with components and other accessories, the safety requirements are achieved, the reliability and maintenance requirements are met, the labeling and other regulatory requirements are met, and the manufacturing, installation, and servicing requirements are met, among other things. Design reviews should be conducted at major decision points during the design phase.

For a large manufacturer, design review provides an opportunity for all those who may have an impact on the quality of the device to provide input, including, manufacturing, quality assurance, purchasing, sales, and servicing divisions. While small manufacturers may not have the broad range of disciplines that may be found in a large company, and the need to coordinate and control technical interfaces may be lessened, the principles of design review still apply. The requirements under section 820.30(e) will allow small manufacturers to tailor a design review that is appropriate to their individual needs.

17 Several comments stated that to demand that every design review be conducted by individuals who do not have direct responsibility for design development is impractical, especially for small companies.

FDA never intended to mandate that an individual without design responsibility conduct the design reviews and, to clarify its position, has rewritten the requirements. The requirement now states that an individual not directly responsible for design development shall be assigned to participate in the design reviews. This requirement will provide an "objective view" from someone not working so closely on the design project, to ensure that the requirements are met. In making this change, FDA also notes that it was not FDA's intention to prohibit those directly responsible for the design from participating in the design review.

18 One comment stated that as part of the systematic design review of the adequacy of the device requirements, and to identify problems with the design, it is occasionally necessary to produce a prototype device and have it evaluated by a physician who is an expert in the area of the device's intended use. Thus, the commentor believed that the regulation should be revised to allow a means for a manufacturer to ship a prototype device to a physician for evaluation.

FDA disagrees with the comment. The regulation does not prohibit the shipment of prototypes for clinical or other studies. Prototypes used in clinical studies involving humans may be shipped in accordance with the IDE provisions in part 812.

19 One comment stated that the wording of section 820.30(e) implies that only one design review is expected, and that design review should be conducted at several stages of product development.

FDA agrees with the comment and has rewritten the requirement to make clear that design reviews must be conducted at appropriate stages of design development, which must be defined in the established design and development plan. This may be one, or more than one, design review, depending on the plan and the complexity of the device.

20 A few comments stated that section 820.30(d), "Design verification," should be rewritten and reordered similar to ISO 9001.

FDA agrees with the comments and has rewritten and reordered this section to be consistent with ISO 9001:1994. The language in revised section 820.30(f) incorporates the requirement of ISO 9001:1994, sections 4.4.7, "Design verification" and 4.4.8, "Design validation."

Under the revised provision, the design must be verified and validated. It is important to note that design validation follows successful design verification, and that design verification is not a substitute for design validation. Design validation should be performed under defined operating conditions and on the initial production units, lots, or batches to ensure proper overall design control and proper design transfer. Design validation may also be necessary in earlier stages, prior to product completion and multiple validations may need to be performed if there are different intended uses.

Proper design validation cannot occur without following all the requirements set forth in the design control section of the regulation.

21 Several comments stated that adequate controls for verification of design output are contained in proposed section 820.30(d), "Design verification," and repeated in proposed section 820.30(f), "Design output." One comment stated that this section will place undue burden on designers and require additional documentation which will add little value to a device's safety and effectiveness.

FDA disagrees with the comments. Revised section 820.30(f), "Design verification and validation" requires verification and validation of the design output. Section 820.30(d), "Design output" requires that the output be documented in a fashion that will allow for verification and validation. These sections thus contain different requirements that are basic to establishing that the design output meets the approved design requirements or inputs, and the user needs and intended uses. Both requirements are essential to assuring the safety and effectiveness of devices. FDA does not foresee these requirements placing undue burden on designers nor requiring additional documentation with no value added. These requirements are considered to be basic requirements to assure the proper performance, and, therefore, the production of safe and effective devices, and are acknowledged and accepted as such throughout the world.

22 Several comments stated that the term "hazard analysis" should be defined in reference to design verification.

FDA has deleted the term "hazard analysis" and replaced it with the definition of "risk analysis." FDA's involvement with the ISO Technical Committee (TC) 210 made it clear that "risk analysis" was the comprehensive and appropriate term, not "hazard analysis." When conducting a risk analysis, manufacturers are expected to identify possible hazards associated with the design in both normal and fault conditions. The risks associated with the hazards should then be calculated in both normal and fault conditions. If any risk is judged unacceptable, it should be reduced to acceptable levels by the appropriate means, for example, by redesign or warnings, among others. An important part of risk analysis is ensuring that changes made to eliminate or minimize hazards do not introduce new hazards. Tools for conducting such analysis include Failure Mode Effect Analysis (FMEA) and Fault Tree Analysis (FTA), among others. The definition rather than the actual term "risk analysis" is used in the regulation because there are several activities and bills currently pending in Congress related to "risk analysis" or "risk assessment" and FDA did not want to confuse its intentions with efforts ongoing in Congress.

23 One comment stated that FDA should provide additional guidance regarding software validation and hazard analysis and what investigators will expect to see.

FDA believes that sufficient domestic and international guidelines are available to provide assistance to manufacturers for the validation of software and risk analysis. For example, "Review Guidance for Computer Controlled Medical Devices Undergoing 510(k) Review," August 1991; "A Technical Report, Software Development Activities," July 1987; and ISO-9000-3 contain computer validation guidance.

24 One comment stated that for some design elements it may be more appropriate to reference data from another prior experimentation rather than conduct new testing, and that the requirement to list verification methods should be modified.

FDA agrees in part with the comment. The revised language of section 820.30(f) will permit the use of data from prior experimentation, when applicable. When using data from previous experimentation, manufacturers must ensure that it is adequate for the current application.

25 A couple comments stated that the requirement for design verification to include software validation and hazard analysis, where applicable, was ambiguous, and may lead an FDA investigator to require software validation and hazard analysis for devices in cases where it is not needed.

FDA disagrees with the comments because software must be validated or verified, and a risk analysis must be conducted, for all devices subject to design controls. FDA believes that such controls are always needed, given the unique nature of software, and that these controls are the minimum necessary to assure that software will perform as intended. FDA has removed the phrase "where applicable."

26 One comment stated that by explicitly mentioning only software validation and hazard analysis as requirements of design verification, FDA was missing the opportunity to introduce manufacturers to some powerful and beneficial tools for better device designs and problem avoidance.

FDA disagrees, because the manufacturer must apply current methods and procedures, appropriate for the device, to verify and validate the device design under the regulation. FDA need not, therefore, list all known methods for meeting the requirements. A tool that may be required to adequately verify and validate one design may be unnecessary (although useful) to verify and validate another

design.

27 One comment questioned whether design verification can be conducted using prototypes or machine shop models.

FDA understands that it is not always practical to conduct clinical studies on finished production units and, therefore, the use of prototypes in clinical studies is acceptable. When prototype designs are used on humans they must be verified as safe to the maximum extent feasible. Full verification of the design, however, cannot be determined by testing prototypes because the actual devices produced and distributed are seldom the same as the prototype. The final verification, therefore, must include the testing of actual production devices under actual or simulated use conditions.

28 Section 820.30(g), "Design transfer" has been revised in response to the many comments objecting to the requirements in this section. Specifically, the proposed requirement for testing production units under actual or simulated use conditions was rewritten and moved to current section 820.30(f), "Design verification and validation."

FDA believes that testing actual production units under actual or simulated use prior to distribution is crucial for ensuring that only safe and effective devices are distributed and has therefore retained the requirement. ISO 9001:1994 discusses this concept in notes 12 and 13. As noted in the immediately proceeding comment, it is not always possible to determine the adequacy of the design by successfully building and testing prototypes or models produced in a laboratory setting. Prototypes may differ from the finished production devices. When moving from laboratory to full-scale production, standards, methods, and procedures may not be properly transferred and manufacturing processes may be added. Often, changes not reflected in the prototype may be made in the product to facilitate the manufacturing process. Proper testing of devices that are produced using the same methods and procedures as those to be used in routine production will prevent the distribution of many unacceptable medical devices. Typically, the confirmation of the device specifications, production methods, and procedures is obtained through process validation and product verification; process validation includes the testing of finished devices under actual or simulated use conditions.

The requirement for testing from the first three production lots or batches has been deleted, however. While FDA believes that three production runs during process validation is the accepted standard, all processes may not be defined in terms of lots or batches. The number three is currently considered to be the acceptable standard because it is said "once is luck, two is a fluke, and three is a trend." Therefore, although the specific number requirement is deleted, FDA expects validation to be carried out properly in accordance with accepted standards, and will inspect for compliance accordingly.

Revised section 820.30(g) now contains a general requirement for the establishment of procedures to ensure that the design basis for the device is correctly translated into production methods and procedures. This is the same requirement that is contained in section 820.100(a) of the current device CGMP regulation.

29 Several comments stated that proposed section 820.30(h), "Design release," was a duplication of requirements in other sections of 820.30 and should be deleted.

FDA agrees in part with the comments and has moved the requirement for design output to be reviewed and approved to the current section 820.30(d), "Design output." The remainder of the requirements have been deleted.

30 A few comments stated that the requirements of section 820.30(h) would prohibit the release of components, partial designs, and production methods before the

design was final because the requirement mandates a review of all drawings, analysis, and production methods before allowing the product to go into production.

FDA did not intend the requirements of section 820.30(h) to prohibit manufacturers from beginning the production process until all design activities were completed. The intent of the requirement was to ensure that all design specifications released to production have been approved and verified or validated before they are implemented as part of the production process. That requirement is now explicitly contained in section 820.30(d).

31 Several comments on section 820.30(i), "Design changes" stated that it is unnecessary to control all design changes and to do so would inhibit change and innovation.

FDA disagrees with the comments. It is not the intent of the regulation to mandate that all design changes be documented and evaluated to the same extent, although they must all be documented and evaluated. The documentation and evaluation should be in direct proportion to the significance of the change. Procedures must ensure that after the design requirements are established and approved, changes to the design are also reviewed, validated (or verified where appropriate), and approved. Otherwise, a device may be rendered unable to properly perform, and unsafe and ineffective. ISO 9001:1994, section 4.4.9, similarly provides that "all design changes and modifications shall be identified, documented, reviewed, and approved by authorized personnel before their implementation."

32 One comment on section 820.30(i) stated that validation of design changes is not always necessary and the regulation should provide for other methods to be used.

FDA agrees with the comments and has amended the requirement to permit verification where appropriate. For example, a change in the sterilization process of a catheter will require validation of the new process, but the addition of chromium to a stainless steel surgical instrument may only require verification through chemical analysis. Where a design change cannot be verified by subsequent inspection and test, it must be validated. The designation for this section is now 820.30(h), since the section on "Design release" has been deleted.

33 Many comments noted that the acronym for design history record (DHR) was the same as that of "device history record" (DHR), and suggested that the name of the "design history record" be changed.

FDA agrees and has changed the name to "design history file" (DHF). The section is now designated as 820.30(i), "Design history file," since the section on "Design release" has been deleted.

34 Several comments stated that the requirements of the "design history record" should be deleted because they were redundant with the requirements of the "device master record" (DMR).

FDA disagrees with the comments. The DMR contains the documentation necessary to produce a device. The final design output from the design phase, which are maintained or referenced in the DHF, will form the basis or starting point for the DMR. Thus, those outputs must be referred to or placed in the DMR. The final design output includes the final device and process specifications and drawings, as well as all instructions, and procedures that are used for purchasing production, installation, maintenance, and servicing. The design history file, in contrast, contains or references all the records necessary to establish compliance with the design plan and the regulation, including the design control procedures. It illustrates the history of the design.

35 A few comments stated that the requirements of the design history record should allow a single design history record for each device family or group having

common design characteristics.

FDA disagrees with the comments and again notes that the intent of the design history file is to document, or reference the documentation of, the actual activities carried out to meet the design plan and requirements of section 820.30. A design history file is, therefore, necessary for each specific design developed. The design history file must provide specific documentation showing the actions taken with regard to each device design, not generically link similar devices together and give an overview of how the output was reached.

36 One comment stated that the requirement that the DHF contain "all" records necessary to demonstrate that the requirements are met should be deleted because not "all" efforts need documentation.

FDA received similar comments on almost every section of the regulation that had the word "all." The requirement does not state that all records must be contained in the DHF, but that all records necessary to demonstrate that the requirements were met must be contained in the file. Such records are necessary to ensure that the final design conforms to the design specifications. Depending on the design, that may be relatively few records. FDA cautions manufacturers who do not document all their efforts that if something is not documented, the information and experience of that effort may be lost, thereby possibly requiring activities to be duplicated or repeated.

<A NAME="pSubpart D">D. Document Controls (Subpart D)</A>

1 One comment stated that Subpart D should be titled "Document controls" instead of "Document and Record Controls" because the "record" requirements are addressed in Subpart M.

FDA agrees and has substituted "controls" for "record."

2 One comment stated that document retrieval of obsolete or unneeded documents should be performed to maintain integrity of the product configuration and the quality system. The commentor suggested adding a requirement for a verification step for document distribution and retrieval to ensure this important element of a quality system is performed correctly.

FDA agrees in part with the comment. The verification of document distribution and retrieval is a very important and can directly affect the quality of a product. The general requirement of section 820.40, which requires that the manufacturer establish and maintain procedures to control all documents, including those that are obsolete and/or to be removed, in conjunction with section 820.40(b), would require that such retrieval (or prevention of use) of obsolete documents be verified.

3 A few comments stated that section 820.40, "Document controls" should be rewritten to be similar to ISO 9001 and to delete the requirement that documents be "accurate," given that commentors feared that violations could be established for typographical errors.

FDA agrees in part with the comments and has rewritten the section, following ISO 9001, to be a general requirement for procedures to control documents that are required under the regulation. The procedures established must ensure control of the accuracy and usage of current versions of the documents and the removal or prevention from use of obsolete documents, among other things, as well as ensure that the documentation developed was adequate to fulfill its intended purpose or requirement. FDA retained the requirement that the procedures ensure that documents are accurate and meet the requirements of the regulation because that is the purpose of controlling the documents. FDA notes that a typographical error can change the intended meaning of a document and have disastrous consequences.

4 Several comments on section 820.40(a), "Document approval and issue," as well as other sections throughout the regulation, suggested that the term "signature" be replaced by the term "identification." Such a change would allow for electronic or computerized identification in lieu of formal written signatures.

FDA is aware that many documentation systems are now maintained electronically, and is in the process of developing an agency-wide policy that will be implemented through rulemaking on the use of electronic signatures. The agency identified several important issues related to the use of such signatures, including how to ensure that the identification is in fact the user's "signature." These issues are discussed in FDA's advance notice of proposed rulemaking on the use of electronic signatures, published in the Federal Register on July 21, 1992 (57 FR 32185) and proposed regulation, published in the Federal Register on August 31, 1994, (59 FR 45160). Therefore, FDA has not revised the regulation to permit "identification," but notes that the Quality System regulation's use of the term "signature" will permit the use of whatever electronic means the agency determines is the equivalent of a handwritten signature when a regulation is finalized.

FDA has, however, revised the requirement in section 820.40(a) to make clear that the documents that must be reviewed and approved are those established to meet the requirements of this part.

5 Several comments stated that section 820.40(b), "Document distribution" should be rewritten to be consistent with ISO 9001.

In response, FDA has deleted the section. The requirements for making documents available at all appropriate locations (ISO 9001:1994 section 4.5.2(a)) and the requirements for promptly removing obsolete documents (ISO 9001:1994 section 4.5.2(b)) have been moved, in revised form, to section 820.40(a). In response to comments, FDA has added that obsolete documents, in lieu of being promptly removed from points of use, may be "otherwise prevented from unintended use."

6 Several comments suggested major changes to section 820.40(c), "Documentation changes." Some stated that the requirements should be revised to be consistent with ISO 9001. Others stated that the requirements related to validation should be rewritten and moved to another section under this part, because this section should only address document changes, not device changes. Several comments stated that the reference to determining whether a 510(k) or PMA is required after making changes to a device should be deleted because it is covered under different parts of the act and regulations.

FDA agrees with many of the comments and has substantially rewritten this section, now designated as section 820.40(b), to relate specifically to changes to a document. The requirements are now very similar to the ISO 9001:1994 requirements in section 4.5.3. FDA has retained the requirement that the approved changes must be communicated in a timely manner to appropriate personnel. FDA has had many experiences where manufacturers made corrections to documents, but the changes were not communicated "in a timely manner" to the personnel utilizing the documents. The result of these untimely communications was the production of defective devices.

In addition, FDA moved the requirement for validating changes to specifications, methods, or procedures to section 820.70(b), "Production and process changes," where it more appropriately belongs.

7 One comment stated that the requirement in section 820.40(c) for changes to be "approved by individuals in the same functions/organizations that performed the original review and approval, unless specifically designated otherwise" is unrealistic and does not reflect the way things are done in real life.

FDA disagrees that the requirement should be deleted and notes that this is a

requirement of ISO 9001:1994 as well. The intent of the requirement is to ensure that those who originally approved the document have an opportunity to review any changes since these individuals typically have the best insight on the impact of the change. The requirement is flexible, however, because it permits the manufacturer to specifically designate individuals who did not perform the original review and approval to review and approve the changes. To designate such individuals, the manufacturer will need to determine who would be best suited to perform the function, thus ensuring adequate control over the changes. In this way, review and approval will not be haphazard.

8 One comment on section 820.40(d), "Documentation change record," stated that this section should be deleted because the other sections adequately covered the proposed requirements. Two comments suggested replacing the section with the requirements of section 4.5.2 of ISO 9001.

FDA has deleted this section and placed the revised requirements in sections (a) and (b). The general requirement of section 820.40 now requires the manufacturer to establish adequate procedures to control all documents required to be established, maintained, and removed. The procedures must cover the specific requirements in sections (a) and (b). Thus, the manufacturer must establish a procedure for ensuring that only the current and approved version of a document is used, achieving the objective of the "list, index, or equivalent document control procedure."

The other requirement in section 820.40(d), "Document change record" was to maintain a record of changes, to include a description of the changes, among other things. FDA has retained this requirement and has moved it into section 820.40(b), "Document changes" because the agency believes this information to be important and useful when investigating and performing corrective or preventative actions.

FDA believes the sections on "Document Controls" now adequately harmonize with ISO 9001:1994 sections 4.5.1, 4.5.2, and 4.5.3.

<A NAME="pSubpart E">E. Purchasing Controls</A>

1 One comment stated that the proposed CGMP regulation omits any discussion of contract reviews, such as that contained in ISO 9001 section 4.3. Rather than leaving these procedures to the interpretations of individual manufacturers and inspectors, the commentor believed that FDA should explicitly state its general policy regarding contract reviews in the regulation.

FDA does not disagree with the contract review requirements of ISO 9001:1994, but believes these provisions are already reflected in requirements within the proposed regulation, such as section 820.50, "Purchasing controls." Therefore, the agency has not added the requirement.

2 One comment stated that the requirements in section 820.50 amount to overregulation. The commentor stated that components are purchased by providing a specification sheet. They are then inspected upon receipt, and defective components are returned. Under section 820.50, the manufacturer would be required to spend more time on paperwork, and product would still have to be inspected upon receipt. Another comment stated that the cost of the quality assurance documentation program is going to be significantly higher for a company who runs a Just In Time (JIT) program than what FDA estimated.

FDA disagrees with the comments. The regulation has been written to allow more flexibility in the way manufacturers may ensure the acceptability of products and services. Under the requirements, each manufacturer must clearly define in the procedures the type and extent of control they intend to apply to products and services. Thus, a finished device manufacturer may choose to provide greater in-.....
house controls to ensure that products and services meet requirements, or to

ensure that the supplier adopts measures necessary to ensure acceptability, as appropriate. FDA believes that, generally, an appropriate mix of supplier and manufacturer quality controls are necessary. However, finished device manufacturers who conduct product quality control solely in-house must also assess the capability of suppliers to provide acceptable product. Where audits are not practical, this may be done through, among other means, historical data, monitoring and trending, and inspection and test data.

FDA notes that the degree of supplier assurance necessary to establish compliance may vary with the type and significance of the product or service purchased and the impact of that product or service quality on the quality of the finished device. If a device manufacturer has established confidence in the supplier's ability to provide acceptable products or services, certification with test data may be acceptable.

Thus, FDA believes that the flexibility of the regulation will allow manufacturers to implement JIT procedures without additional cost. In fact, the new regulation is more conducive to JIT practices by requiring the assessment or evaluation of product or services up front, thereby lessening the degree of in-house control that may be necessary, as compared to emphasizing incoming test and inspection under the current CGMP requirements.

3 One comment stated that "manufacturing materials" should be deleted from the first sentence of this section as the assessment of the manufacturers of manufacturing materials would be a monumental task.

FDA disagrees with the comment. The first sentence of section 820.50 is rewritten to be a general requirement that each manufacturer must establish procedures to ensure that received product and services (purchased or otherwise) conform to specified requirements. All manufacturers are expected to apply controls to manufacturing materials appropriate to the manufacturing material, the intended use, and the effect of the manufacturing materials on safety and effectiveness. For example, the procedures necessary to ensure that a mold release agent conforms to specified requirements may be less involved than the procedures for controlling latex proteins. The provision allows the manufacturer the flexibility of establishing the procedures to meet its needs and to ensure that the product conforms to specified requirements.

4 Several comments said that it was unclear what FDA meant by the phrase "or held by other persons under contract conform to specifications" and that this phrase should be deleted.

FDA agrees with the comments and has deleted the phrase. The phrase was intended to mean devices and components which were purchased or processed in some manner by other organizations. Section 820.50 now applies to "purchased or otherwise received product" to convey this meaning. FDA emphasizes that the requirements apply to all product received from outside of the finished device manufacturer, whether payment occurs or not. Thus, a manufacturer must comply with these provisions when it receives product or services from its "sister facility" or some other corporate or financial affiliate.

5 One comment said that FDA should delete the last sentence of general section 820.50 because it is unnecessary for manufacturers to develop specifications for services that are unrelated to product or process quality, and because the terms "service" and "other persons" lack definition.

FDA disagrees. First, as used in the regulation, "service" means parts of the manufacturing or quality system that are contracted to others, for example, plating of metals, testing, and sterilizing, among others. Second, FDA believes that all suppliers of such a service must be assessed and evaluated, just like a supplier of a good or product. As always, the degree of control necessary is related to the

product or service purchased. FDA has, however, deleted the term "provided by other persons" because it was unnecessary.

6 One comment stated that many suppliers of components to the medical device industry have their quality systems certified to an ISO 9000 standard by an independent third party auditor, and that such registration of component manufacturers should be considered in vendor assessment plans.

FDA agrees in part with the comment in that certification may play a role in evaluating suppliers, but cautions manufacturers against relying solely on certification by third parties as evidence that suppliers have the capability to provide quality products or services. FDA has found during inspections that some manufacturers who have been certified to the ISO standards have not had acceptable problem identification and corrective action programs. Therefore, the initial assessment or evaluation, depending on the type and potential effect on device quality of the product or service, should be a combination of assessment methods, to possibly include third party or product certification. However, such assessment or evaluation may not be relied on exclusively.

7 FDA added consultants to section 820.50(a) in response to the comments from section 820.25(c).

8 One comment on section 820.50(a) stated that listing all suppliers and maintaining documented supplier assessment criteria is an excessive requirement for certain low risk components and manufacturing materials. The commentor stated that it is appropriate for the manufacturer to establish a documented, justified supplier quality program based on risk. Another comment stated that the requirement would require manufacturers to assess all potential suppliers which would place many small and medium size firms under extreme duress. Another comment stated that section 820.50(a) is open to interpretation that all suppliers and contractors must undergo either on-site or "paper" assessment of their quality system and that some suppliers may not be willing to undergo an assessment, even though they supply a material critical to the performance of a device.

After evaluation of all of the comments on section 820.50, FDA has decided to change the wording of section 820.50(a) and adopt the wording of ISO 9001 to make clear that manufacturers have flexibility in determining the degree of assessment and evaluation necessary for suppliers, contractors, and consultants. In addition, the requirement for manufacturers to establish assessment criteria has been modified. Each manufacturer must now define the type and extent of control it will exercise over suppliers, contractors, and consultants. This is consistent with the 1994 version of ISO 9001.

The type and extent of the controls that would be required may vary with the difficulty of the service, the importance of the product or service, and the impact the product or service may have on the safety and performance of the device. For example, the extent of control that must be exercised over products and contract services that are significant to the proper functioning and safety of the device would be greater than that which may need to be exercised over less significant product or services. The controls applied should include on-site auditing, where feasible and appropriate. However, other means such as receiving inspection and test, evaluation of past history, or monitoring of incoming quality, depending on product and service, may be acceptable. Typically an appropriate mixture of assessment and incoming inspection and test is necessary for proper control.

9 One comment said that requiring evaluation of potential suppliers, contractors, and consultants "on the basis of their ability to meet requirements" is vague and should be clearly defined.

FDA disagrees that the phrase is vague. Suppliers, contractors, and consultants selected by manufacturers of medical devices should have a demonstrated capability of providing products and services that meet the requirements

established by the finished device manufacturer. The capability of the products or services should be reviewed at intervals consistent with the significance of the product or service provided and should demonstrate that they conform to specified requirements.

10 One comment questioned the usefulness of section 820.50, given that the requirements under section 820.80, "Receiving, in-process, and finished device acceptance" require manufacturers to establish and maintain procedures for acceptance of incoming components.

The intent of section 820.50 is to ensure that device manufacturers select only those suppliers, contractors, and consultants who have the capability to provide quality product and services. As with finished devices, quality cannot be inspected or tested into products or services. Rather, the inherent quality of a product or service is established during the design of that product or service, and achieved through proper control of the manufacture of that product or the performance of that service. Section 820.50 thus mandates that products be manufactured and services be conducted under appropriate quality assurance procedures. Finished device manufacturers are required under section 820.50 to establish the requirements for, and capability of, suppliers, contractors, and consultants to provide quality products and services.

Section 820.80 is specific to a device manufacturer's incoming inspection and test (or "acceptance") program. While finished device manufacturers are required to assess the capability of suppliers, contractors, and consultants to provide quality products and services, inspections and tests, and other verification tools, are also an important part of ensuring that the finished device conforms to approved specifications. The extent of incoming acceptance activities can be based in part on the degree the supplier has demonstrated a capability to provide quality products or services. An appropriate product and services quality assurance program includes a combination of assessment techniques. Inspection and test is just one method which can be utilized to the extent appropriate for the significance of the device and the impact the product or service has on the safety and performance of the finished device.

11 One comment stated that it was not clear how a manufacturer could evaluate an off-the-shelf component that is purchased from a distributor rather than directly from its manufacturer, and stated that it would not be helpful to audit the distributor.

FDA agrees that auditing a distributor would not meet the intent of section 820.50. Manufacturers should remember that the purpose of assessing the capability of suppliers is to provide quality products and to provide a greater degree of assurance, beyond that provided by receiving inspection and test, that the products received meet the finished device manufacturer's requirements. The agency recognizes that finished device manufacturers may not always be able to audit the original manufacturer. In such cases, the manufacturer must apply other effective means to assure that products are acceptable for use.

12 Many comments from both domestic and foreign firms in response to proposed section 820.22(b) said that making supplier audit reports subject to FDA review will have a major adverse impact on the relationships between the finished device manufacturers and their suppliers and service providers. Some stated that the requirement will cause suppliers to refuse to sell components to medical device manufacturers, especially suppliers who provide only a small part of their production to device manufacturers. Others said that this policy is not consistent with FDA's policy for internal audits.

FDA recognizes that quality audits of suppliers have a significant and demonstrated value as a management tool for corrective action, quality improvement, and overall assurance of component and service quality, and does not seek to undermine their value. Therefore, based on the concerns raised by the

comments, FDA will not at this time review supplier audit reports during a routine FDA inspection for compliance with this part, as noted in section 820.180(c), "Exceptions." As noted in response to earlier comments, FDA intends to revisit this decision in the future. The audit procedures and assessment criteria, the evaluation procedures, and other documents that demonstrate conformance with section 820.50 will be subject to review by an FDA inspector.

13 One comment stated that it was unclear what is meant by the requirement to specify "quality requirements" that must be met for suppliers, contractors, and consultants, as stated in section 820.50(a).

The term "quality requirements" means the quality control and quality assurance procedures, standards, and other requirements necessary to assure that the product or service is adequate for its intended use. FDA does not believe the term is unclear.

14 Several comments on section 820.50(b), "Purchasing forms" suggested that the term "forms" be replaced by "data." Other comments stated that use of the term would not allow electronic data exchange. One comment stated that the use of an exclusive form for purchasing is unnecessary and redundant, and that it is unduly burdensome to require detailed documentation on those commonly available items such as fasteners. The comment stated that it is common practice to use prints or drawings to fulfill the purpose of the form.

FDA agrees in part with the comments, but does not believe that section 820.50(b) prohibits the use of drawings or prints, assuming that the documents contain data clearly describing the product or service ordered, and that the specified requirements are met. However, section 820.50(b) has been rewritten and now requires manufacturers to establish purchasing "data." This provides each manufacturer with the flexibility to use both written and electronic means to establish purchasing information.

15 One comment stated that the inclusion of an additional provision mandating that suppliers notify manufacturers of any change in their product or service places an undue burden on suppliers and inhibits their ability to make minor adjustments within the parameters of agreed upon specifications and quality requirements. Many other comments stated that the requirement of section 820.50(b) is feasible only for components that are custom made for the manufacturer, and is meaningless for off-the-shelf components purchased from distributors. Other comments state that the requirement is part of the current CGMP regulation and experience has shown that suppliers are not willing to supply device manufacturers with such information.

FDA agrees in part with the comments and has amended the requirement to state that such agreement must be obtained "where possible." FDA still believes that this change information is very important to the manufacturer, and that the manufacturer should obtain information on changes to the product or process. Where a supplier refuses to agree to provide such notification, depending on the product or service being purchased, it may render him an unacceptable supplier. However, where the product is in short supply and must be purchased, the manufacturer will need to heighten control in other ways.

16 One comment stated that section 820.50(b) should incorporate a provision that the manufacturer may cite published standards in purchasing forms as one suitable method for specifying purchased item quality requirements.

That addition is unnecessary, in FDA's estimation, because the regulation permits manufacturers to clearly describe or reference requirements. A reference could be to a standard.

17 One comment stated that it is unclear whether the requirement for a signature to approve purchasing documents pertains to approval of the form used for

purchasing or approval of the individual purchasing transaction. The comment also stated that a signature approval by transaction is not practical for firms using electronic document transmittals.

FDA has rewritten the requirement to be more clear. The requirement is for approval of purchasing data or information used to purchase a product or service. Thus, each manufacturer must review and approve the purchasing data before release of the data. FDA addressed the use of electronic signatures in response to another comment, and notes briefly that FDA is in the process of developing an agency-wide policy on the use of electronic signatures.

18 One comment stated that purchasing is carried out verbally in many small firms, without the use of component-specific purchasing forms, and that the regulation should be revised to allow such verbal purchasing to continue.

FDA disagrees with the comment. About 15 percent of the recalls each year are due to unacceptable purchased products. Many of these products are unacceptable because the finished device manufacturer did not properly describe the product. The requirements for purchased products and services must be documented to ensure that the supplier, contractor, and consultant provide a product or service which conforms to specified requirements. This requirement, and the goal it seeks to achieve, are applicable to both small and large companies.

19 One comment stated that the requirement that purchasing forms spell out the specifications for manufacturing materials in all cases is excessive, and that the need for specifications should be based on the criticality of and risk associated with the use of the specific manufacturing material.

FDA agrees that the specifications for many manufacturing materials may be so well established that the trade name of the product may be sufficient to describe the material needed. For other materials, specific written specifications may be necessary to ensure that the materials desired are received. The extent of the specification detail necessary to ensure that the product or service purchased meets requirements will be related to the nature of the product or service purchased, taking into account the effect the product or service may have on the safety or effectiveness of the finished product, among other factors. The term "specification" has been replaced with the term "specified requirements" to better reflect the intent of the requirement.

<A NAME="pSubpart F">F. Identification and Traceability (Subpart F)
i. Identification

1 A few comments on sections 820.60, "Identification and traceability" and 820.65, "Critical device, traceability" stated that the two sections should be rewritten to delete the distinction between critical and noncritical devices. Some stated it should be consistent with ISO.

FDA agrees in part with the comments and has rewritten section 820.60 to be consistent with ISO 9001:1994. The term "critical device" is also deleted, and traceability, where necessary to assure the protection of the public health, is addressed solely in section 820.65.

2 One comment stated that manufacturing materials should be deleted from section 820.60, as the requirements are excessive and not cost justifiable with regard to such materials.

FDA disagrees with the comment. The purpose of section 820.60 is to ensure that all products, including manufacturing materials used in the manufacture of a finished device, are properly identified as to their current status, for example, whether they are accepted, rejected, or reworked. This requirement is intended to help prevent inadvertent use or release of unacceptable product into manufacturing. It is as important that the proper manufacturing materials be used

as it is that the proper component be used.

ii. Traceability

1 A few comments state that section 820.65, "Critical devices, traceability" implies that traceability requirements exist for all devices.

As noted above, FDA has deleted the critical device terminology and distinction in response to comments requesting such deletion, and section 820.65 is now entitled "Traceability." The revised section tracks the language of the act, and requires that a manufacturer be able to trace, by control number, any device where necessary to assure the protection of the public health. See Section 520(j) of the act (21 U.S.C. 360j(j)). Such products would include those whose failure could result in serious injury or harm to the user. At a minimum, traceability would be required for the critical devices as defined and listed in the Federal Register Notice of March 17, 1988, and for in vitro diagnostic products (21 CFR 809.10(a)(9)), due to the specific nature and individuality of the reagents used. This change is also consistent with the overall changes to the CGMP regulation that were proposed on November 23, 1993. The new CGMP regulation would not distinguish between devices, but makes many of the requirements previously applicable only to critical devices applicable to all devices, but provide the manufacturer the ability to tailor its procedures to the specific device being manufactured. FDA will notify a manufacturer directly, by letter, when it determines that a device of that manufacturer is subject to the traceability requirement. Manufacturers may find it advantageous, however, to provide lot, unit, or batch traceability for devices for which traceability is not a requirement to facilitate control and limit the number of devices that may need to be recalled due to defects or violations of the act.

2 Another comment on section 820.65 stated that critical device component traceability could be interpreted to be required for almost all electronic components and other components in a critical device. The commentor stated that the extent of component traceability should be left to the manufacturer's discretion, since it is an economic risk decision.

FDA disagrees that the traceability determination should be based solely on economic risk. As noted in the preamble to the November 23, 1993, proposal (58 FR 61964), where traceability is important to prevent the distribution of devices that could seriously injure the user, traceability of components must be maintained so that potential and actual problem components can be traced back to the supplier.

The revised requirement mandates traceability of components where necessary to assure the protection of the public health. The critical component definition in the current CGMP regulation may be used as guidance. However, to carry out the requirement of the revised provision, the manufacturer should perform risk analysis first on the finished device, and subsequently on the components of such device, to determine the need for traceability. Both FDA and the authors of ISO/DIS 13485 believe that the extent of traceability for implantable devices should include all components and materials used when such products could the medical device not to satisfy its specified requirements.

<A NAME="pSubpart G">G. Production and Process Controls (Subpart G)</A>

i. Production and process controls

1 A few comments stated that the requirements in section 820.70(a), "Production and process control" are similar to those in ISO 9001, but that ISO 9001 makes clear that the requirements apply only "where applicable" and where deviations from device specifications would "directly affect quality." The comments suggest that FDA similarly employ such language to avoid being too restrictive and overly burdensome.

The requirements in section 820.70(a) are intended to ensure that each

manufacturer produces devices that conform to their specifications. Thus, where any deviations from specification could occur during manufacturing, the process control procedures must describe those controls necessary to ensure conformance. Those controls listed may not always be relevant; similarly others may be necessary. For example, where deviations from device specifications could occur as a result of the absence of written production methods, procedures, and workmanship criteria, such production controls are required. Thus, FDA has retained the provision, but revised it slightly to conform to current section 820.100(b)(1).

As noted, the process controls requirement applies when any deviation from specifications could occur. FDA believes that such deviations must be controlled, and that linking the requirement to deviations that directly affect quality is inappropriate and subjective, and that it could lead to the manufacture of potentially dangerous devices through the lack of control of processes known to directly affect a device's specifications. Therefore, the provision has not been restricted in this manner.

2 One comment stated that the second sentence of proposed section 820.70(a) was too restrictive, in that some processes can be accomplished by adequately trained personnel without the use of procedures.

FDA disagrees with the comment because the establishment of procedures is intended to ensure consistency in manufacture. The procedures may be tailored under the requirement, as written, to cover only those controls necessary. The procedures must describe whatever process controls are necessary to ensure that a device meets its specifications. FDA notes that the deletion of the word "all" does not alter the requirements; all processes must be controlled wherever any deviations could occur.

In addition to these changes, FDA has added the requirement that production processes be "monitored" because a manufacturer must continually monitor a controlled process to ensure that the process remains in control.

3 FDA deleted the requirement for process controls related to "installation and servicing" from section 820.70(a)(1) and (2) in response to comments. Such control is adequately assured by the requirements in sections 820.126, "Installation" and 820.200, "Servicing."

4 One comment noted that there is no longer a requirement that process changes be validated.

Revised section 820.70(b), "Production and process changes," addresses the requirement for production and process changes to be validated, except where the change is fully verified. This requirement for validation was moved from section 820.40(c), in revised form, to this section. Verification of changes was added to give the manufacturer the flexibility to verify changes that can be tested and inspected because FDA believes that validation is not always necessary. FDA has provided guidance on when changes are expected to be validated in its "Guideline on General Principles of Process Validation." The agency notes that wherever variables may influence a process, the process must be validated. A few examples of processes that must be validated include sterilization, molding, and welding.

5 The EU Commission stated that environmental conditions only affect the quality of certain devices and that the requirements should, therefore, be restricted in their application. Other comments stated that the requirements in section 820.70(b), "Environmental control" were not consistent with the requirements in current CGMP section 820.46.

FDA agrees that environmental controls must be established where necessary to control adverse effects and believes that the regulation was restrictive in its application by requiring that a control system be established that would "prevent

contamination or other adverse effects." However, FDA has revised the provision, to clarify it and to better harmonize with the working draft of ISO/DIS 13485.

In harmonizing, FDA has added the requirement in newly designated section 820.70(c), "Environmental controls," for the manufacturer to establish and maintain requirements for the environment to which product is exposed. FDA believes such a requirement is a necessary precursor to the requirement for controlling the environmental conditions that could have an adverse effect on the device.

The requirements for procedures to ensure control of conditions, periodic inspection of control systems, and documentation and review of results are similar to the existing CGMP requirements. However, the specific list of conditions to be considered for control, which were carried over from the CGMP regulation to the proposal, were deleted in response to a comment from the Global Harmonization Task Force that the list would be better suited for a guidance document. FDA agrees that it is not necessary to give examples of conditions that may need controlling in a regulation, and notes that lighting, ventilation, space, temperature, humidity, air pressure, filtration, airborne contamination, and static electricity are among many conditions that should be considered for control.

6 One comment stated that the last sentence of section 820.70(b) should be deleted because it is redundant with the audits required in section 820.22(a). Another comment said that environmental conditions are currently reviewed via internal audit, which an FDA inspector cannot review.

FDA disagrees with the comments. The inspection and review of environmental control systems are routine quality assurance functions that are part of the production quality assurance program. The audits required by section 820.22(a) are audits of the quality system, conducted to ensure the adequacy of and conformance with the quality system requirements. The requirement to conduct a quality audit is in addition to other provisions in the regulation which require that a manufacturer review its specific controls, among other things, to ensure the requirements are met. FDA may review and copy the inspection results of environmental control systems.

7 The Global Harmonization Task Force commented that the requirements of section 820.70(c), "Cleaning and sanitation" should be placed in guidance.

After careful consideration, FDA agrees that a separate section on cleaning and sanitation is unnecessary. The objective of section 820.70(c) is adequately met through the requirement of section 820.70(e), "Contamination control," and 820.70(a), the general process control procedure requirement. Contamination control must include establishing and maintaining adequate cleaning procedures and schedules, if such control is necessary to meet manufacturing process specifications. In addition, section 820.25, "Personnel" requires that employees have a thorough understanding of their job functions, which would include a requirement that the appropriate employees comprehend the cleanliness and sanitation procedures.

8 The Global Harmonization Task Force and others commented that the specific requirements of proposed subsections 820.70(d)(1) through (3) should be deleted and placed in guidance because they are redundant with the first sentence in section 820.70(d), "Personnel health and cleanliness."

FDA agrees with the comments and has deleted the subsections. FDA has also rewritten the section now entitled "Personnel" to require procedures to achieve the desired result, rather than dictate the means to achieve the result. The section as rewritten thus provides the manufacturer more flexibility and is consistent with the working draft of ISO/DIS 13485. Under this section, a manufacturer's requirements must not permit unclean or inappropriately clothed employees, or employees with medical conditions, to work with devices where such conditions

could adversely effect the quality of the product. The requirements must also establish acceptable clothing, hygiene, and personal practices, as applicable to the device being manufactured.

FDA also added the requirement, from ISO/DIS 13485, that personnel who are working temporarily (such as maintenance and cleaning personnel) under special environmental conditions (such as a clean room) be appropriately trained or supervised by someone trained to work in such an environment.

9 One comment stated that the requirements of section 820.70(e), "Contamination control" should be deleted and placed in guidance.

FDA has rewritten the section to delete the specific references to contaminants that probably gave rise to the suggestion that the section would be more appropriate as guidance. The section now contains a broad requirement for the establishment of procedures to prevent contamination of equipment or product by any substance (whether hazardous, contaminants generated by the manufacturing process, or otherwise) that could adversely affect the device. Again, this revision adds flexibility.

10 One comment on section 820.70(e), "Contamination control" stated that the reference to manufacturing materials should be deleted because it is redundant with section 820.70(g), "Equipment."

FDA disagrees with the comment because section 820.70(e) requires procedures to ensure that manufacturing materials do not become contaminated. The section still contains the requirement for manufacturing materials contamination control through use of the new term "product," which includes manufacturing material. Section 820.70(g), in contrast, establishes requirements related solely to the equipment used in the manufacturing process. And section 820.70(h), "Manufacturing material," addresses requirements for the removal or limitation of manufacturing materials which could adversely affect the device. Thus, these sections are distinct and are intended to achieve different objectives.

11 One comment on proposed section 820.70(b), "Environmental controls" requested that FDA delete reference to "facilities" inspection and limit the requirement to review of the control system, as currently contained in the CGMP regulation.

In response, FDA reworded the requirement for the inspection to be related to the control systems required by revised section 820.70(c), "Environmental Control." This requirement mandates that the control system at the facility actually be inspected. FDA has, however, added a new section 820.70(f), "Buildings," that requires that buildings be of suitable design and contain sufficient space to allow for the proper manufacture of devices. The section is worded similarly to the existing CGMP regulation section 820.40, and is intended to achieve the same objectives as that section.

12 The only two comments received on proposed section 820.70(f), "Sewage and refuse disposal," recommended that the section be deleted because it was unnecessary and/or covered by other federal regulations.

The section has been deleted because the requirements are adequately covered in the current requirements under sections 820.70(e), "Contamination control" and 820.70(c), "Environmental control." Pursuant to these sections, sewage, trash, byproducts, chemical effluvium, and other refuse that could affect a device's safety, effectiveness, or fitness for use must be adequately controlled and disposed of.

13 Two comments stated that the requirement related to equipment in section 820.70(g) should ensure that equipment meets "specified requirements" not be "adequate for its intended use" because intended use is determined during the design phase, and because it is easier to assess whether equipment meets specified requirements.

From these comments, FDA can see that the requirement should be revised because it may have been misinterpreted. The requirement is reworded as suggested. Under the requirement, the equipment must be appropriately designed to facilitate maintenance, adjustment, cleaning, and use. It must also meet the requirements that are necessary to ensure its proper functioning for the manufacture of the device. Hence, it must be "adequate for its intended use."

14 A few comments stated that not all equipment requires maintenance, and the requirement for a maintenance schedule in section 820.70(g)(1) should be revised to make that clear.

FDA agrees that not all equipment may require maintenance and notes that the general requirement of section 820.70(a) requires process control procedures that describe those controls which are necessary. Therefore, FDA did not revise the requirement.

15 The Global Harmonization Task Force recommended that the second sentence of section 820.70(g)(1), which requires that the maintenance schedule be posted or readily available, be deleted and placed in guidance.

After consideration of the application of the requirement, FDA has deleted the requirement. The requirement under general section 820.70(g), for a manufacturer to ensure that equipment meets specified requirements, would require that the manufacturer ensure that maintenance is carried out on schedule to comply with the requirement. FDA expects that the schedule, to satisfactorily meet this requirement, would be posted on or near the equipment to be maintained, or otherwise made readily available to appropriate personnel. Deletion of the requirement, however, permits the manufacturer added flexibility in ensuring that the requirement is met.

16 One comment stated that companies are moving to computerized systems to schedule and document preventative maintenance and that the requirement for a "written record" in the third sentence of section 820.70(g)(1) should, therefore, be revised.

FDA agrees and has amended the requirement to require "[r]ecords," permitting the use of written or electronic recording, pursuant to section 820.3(x).

17 Several comments stated that sections 820.70(g)(2), "Inspection," and 820.70(g)(3), "Adjustment," should be deleted and placed in guidance because the requirements are adequately covered under the requirements in section 820.70(g)(1).

FDA believes that to adequately ensure that equipment continues to meet its specifications, and to ensure that inherent limitations and allowable tolerances are known, these specific requirements are imperative. Both of these sections are requirements in the CGMP regulation currently and the agency has found them to be both useful and necessary.

18 One comment stated that requiring the removal of manufacturing material to be documented in proposed section 820.70(g)(4), "Manufacturing material" will result in impossible requirements, such as the requirement to document how much cutting oil is lost during a metal removing operation, such as drilling.

FDA disagrees because the section (now section 820.70(h)) merely requires that the fact that manufacturing material was removed be documented, not how much was removed or how much was lost due to processing. This requirement is carried over from the current device CGMP regulation, section 820.60(d).

19 One comment on section 820.70(h), "Automated processes," (now section 820.70(i)) stated that the section should be revised to reflect that software used in

such systems must be validated for "its intended use," not simply validated. Another comment stated that most companies buy software currently available on the market and do not make changes to the software. It was recommended that this section allow for use of outside personnel for validation runs and not necessarily require the development of a software validation procedure. Related to commercially available software, one comment suggested that the section should allow verification rather than validation.

FDA has modified the requirement to mandate validation for the intended use of the software. In addition, the requirement that the software be validated by individuals designated by the manufacturer has also been deleted to make clear that validation may be performed by those other than the manufacturer. However, whether the manufacturer designates its own personnel or relies on outside assistance to validate software, there must be an established procedure to ensure validation is carried out properly.

FDA has maintained the requirement for validation, however, because the agency believes that it is necessary that software be validated to the extent possible to adequately ensure performance. Where source code and design specifications cannot be obtained, "black box testing" must be performed to confirm that the software meets the user's needs and its intended uses.

FDA emphasizes that manufacturers are responsible for the adequacy of the software used in their devices, and activities used to produce devices. When manufacturers purchase "off-the-shelf" software, they must ensure that it will perform as intended in its chosen application.

20 Several comments on "automated processes" stated that the term "data processing systems" was unclear and its inclusion rendered the requirement too broad.

FDA disagrees. The phrase "automated data processing" is contained in the current device CGMP regulation under section 820.195, "Critical devices, automated data processing" and has not been misunderstood or considered to be unclear. Software used in data processing systems, whether it be in the designing, manufacturing, distributing, tracking, or quality system areas, must be validated.

ii. Process validation

1 A few comments on proposed section 820.75, "Special processes" stated that the meaning of the term "special processes" was unclear. Other comments stated that FDA should provide examples of processes that would be considered "special processes."

In response to the comments, the term "special processes" has been dropped from the regulation. The section now requires that all processes which cannot be fully verified by an inspection and test method be validated. Examples of such processes include sterilization, aseptic processing, injection molding, and welding, among others. As the explanation for section 820.70(b), "Production and process changes" noted, whenever variables exist in a process, the process must be validated. The validation process used under this requirement must ensure that predetermined specifications are consistently met. The new section, entitled "process validation" is consistent with ISO 9001:1994.

2 Several comments were received on parts (1) through (4) of section 820.75 that stated that the requirements were redundant to other parts of the regulation and should be modified or deleted.

FDA disagrees with the comments and believes that, due to the importance of process validation and correct performance of the process validated, the requirements are necessary. The requirements have been rearranged in the revised section.

3 Comments on the first sentence of section 820.75(b) stated that the intent was

unclear and unrealistic.

Given that it was believed by commentors to be unclear, FDA has revised the requirements. The section's requirements (as proposed and as revised) apply to the performance of a process after the process has been validated. In contrast, section 820.75(a) relates to the actual validation of the process. The revised section, which is now section 820.75(d), requires that the dates on which the process was performed, the person performing it, and the major equipment used, where appropriate, be documented. In addition, section 820.75(d) requires that monitoring and control methods and data be recorded. FDA believes that the new arrangement of section 820.75 should clear up any confusion.

FDA notes that it is always "appropriate" to document the equipment used in the process where the manufacturer uses different equipment on different manufacturing lines. To investigate a problem with the device, the manufacturer will need to know which tester was used, since the problem could be with the equipment itself, rather than the device.

<A NAME="pSubpart H">H. Acceptance Activities (Subpart H)</A>

i. Receiving, in-process, and finished device acceptance

1 One comment stated that the emphasis on testing and inspection in section 820.80 completely ignores the quality goals, the benefit of requiring purchasing controls, and statements made in the preamble of the proposal reflecting FDA's negative opinion about manufacturers relying solely on testing and inspection.

FDA agrees with the comment and has replaced the term "inspection and test" with "acceptance activities" in section 820.80. Further, FDA defines "acceptance activities" to include inspections, test, and other verification activities, such as an appropriate mix of supplier audits and inspection and test. In addition, with a documented history of acceptable received product or services from a supplier, the degree of inspection and test necessary may change.

2 One comment stated that recordkeeping is a significant cost factor in the operation of a total quality system, and that the revised CGMP regulation should not add cost through duplication of documentation. The comment said that the requirement to record all quantitative data seems inappropriate and of little value.

FDA agrees that one goal of a quality systems regulation should be to avoid unnecessary duplication of documentation. FDA believes that the proposed quality system regulation requires the minimum documentation necessary to ensure that safe and effective devices are designed and produced. FDA similarly believes that maintaining records of results of acceptance activities is imperative to ensuring that nonconforming product is not used or distributed. FDA has, however, deleted the requirement for recording the results of inspections and testing from section 820.80(a) because section 820.80(e) requires that the results of all acceptance activities be recorded. The requirement in subsection (a) was therefore unnecessary.

3 Several comments stated that proposed section 820.80(b), "Receiving inspection and testing," did not allow for urgent use of incoming items. The comments said that urgent use should be permitted if forward traceability is maintained so that recall and replacement is possible if the material is subsequently found to be nonconforming.

FDA agrees in part with the comments because FDA has permitted manufacturers to use incoming items that had not yet been proven acceptable for use, provided that the manufacturer maintained control of the unapproved items and could retrieve the product that contained the unapproved items before distribution. Therefore, the requirement that product "shall not be used or processed until ... verified" is deleted from section 820.80(b), now entitled "Receiving acceptance activities." However, FDA emphasizes that while the product can be used in production prior to verification, it cannot be distributed prior to verification. FDA

will not permit the distribution of unapproved product through an urgent use provision.

4 One comment stated that the requirements in section 820.80(b) were too specific and did not allow flexibility.

In addition to the changes noted above, FDA has deleted the requirement that "individual(s) designated by the manufacturer shall accept or reject incoming" product. FDA does not believe this requirement is necessary in section 820.80(b) because section 820.80(e) requires that the identification of the individual(s) conducting the acceptance activities be recorded.

5 Several comments stated that an absolute requirement under proposed section 820.80(c), "In-process inspection and testing," for in-process testing is inconsistent with the preamble, which states that an appropriate mix of controls should be established. Other comments stated that in-process inspection and testing is unnecessary if the process is validated and the devices are subject to final inspection.

FDA agrees with the comments in part, but believes that the section as now written does not mandate in-process inspection and testing. The requirement states that in-process product must be held until the required inspection and test, or other verification activities, have been performed. FDA acknowledges that in-process acceptance activities may not be necessary for every device, for example, medical socks.

6 FDA received a similar comment on proposed section 820.80(d), "Final inspection and test," which said that the provision requires finished device inspection for all devices, without defining what inspection is expected. It was alleged that the section would be interpreted as requiring actual product inspection, which has been shown to be ineffective as a means of controlling product quality.

FDA has rewritten section 820.80(d) to require that manufacturers establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meet specified requirements. Manufacturers have the flexibility to choose a combination of methods, including finished device inspection and test, provided such methods will accomplish the required result.

7 One comment stated that signatures should not be the only approved method for identification of the individual(s) responsible for release. The commentor stated that use of inspection stamps and individual's initials should be allowed.

FDA believes that it is important for the person responsible for release to have personally documented and dated that release. This cannot be determined through use of an inspection stamp. FDA has retained the requirement for a signature.

8 Several comments on proposed section 820.80(e), "Inspection and test records" stated that manufacturers should not be required to record the use of general equipment in inspection and test records, because this requirement would be burdensome to large manufacturers who use many common pieces of equipment.

FDA agrees that it may not be necessary to document every piece of equipment used in acceptance activities. The requirement now provides that equipment used shall be documented "where appropriate." For some critical operations and testing, identification of the equipment used will be imperative for proper investigations into nonconforming product.

9 One comment stated that the record requirements under section 820.80(e) are overly prescriptive and go well beyond ISO 9001's comparable requirements. The commentor stated that recordkeeping should be specified by the manufacturer in the spirit of ISO 9001, and should include only the minimum records necessary to show that finished device inspections are performed in accordance with established

procedures.

The requirements, as revised, are similar to those required under ISO 9001:1994. Certain information must be captured on acceptance records for the records to be useful in evaluating nonconformance. Through many years of experience, FDA has determined what information it believes to be a minimum requirement for these records. Section 820.80(e) reflects that determination.

ii. Inspection, measuring, and test equipment

1 One comment stated that it is unclear what is meant by the requirement in section 820.84, "Inspection, measuring, and test equipment" that equipment be capable of producing "valid results." The comment stated that such equipment may be "suitable for its intended purpose" and still not always "produce valid results."

FDA believes that the term is commonly understood and notes that it has been in the CGMP regulation under section 820.61 for 15 years. The requirement is for the equipment to work properly, thereby providing "valid results."

FDA revised the requirement to make clear that the procedures must also ensure that the equipment is maintained.

2 A few comments stated that the last sentence in section 820.84(a), "Calibration" is unnecessary because the requirement for trained personnel is redundant with section 820.25(a), "Personnel."

FDA agrees and has deleted this sentence.

3 Several comments stated that section 820.84(b), "Calibration standards" should allow for the use of international standards.

FDA agrees and has rewritten the section to allow for the use of international standards. The standards used must be generally accepted by qualified experts as the prevailing standards.

4 FDA has deleted the requirement in section 820.84(c) for calibration records to be "maintained by individuals designated by the manufacturer" because, on further reflection, the agency believes such a requirement is unnecessary. As long as the required records are maintained and displayed or readily available as required, the objective of the section, ensuring that calibration is performed and acceptable, will be met.

5 Two comments suggested deleting section 820.84(d) because they believed it was unnecessary to establish procedures to maintain equipment, since most manufacturers simply store equipment in protective covers.

As already noted, FDA has moved the requirement for establishing maintenance procedures into the general requirement in section 820.84. FDA has retained the specific requirements for the maintenance procedures, however, because some equipment requires special handling, preservation, and storage. For example, the temperature and humidity of a room may affect the equipment and procedures would need to be established taking those factors into account.

FDA has added the requirement for the maintenance of test software in section 820.84(d) to be consistent with ISO 9001:1994, section 4.11.1.

6 Several comments stated that proposed section 820.84(e), "Facilities" should be deleted because it is redundant with the requirements under section 820.70(g) and the general requirements of section 820.84.

FDA agrees that general section 820.84 would require procedures to ensure that equipment is protected from adjustments that could invalidate the calibration, in that the section requires procedures to ensure that equipment is properly

maintained. This maintenance must ensure that equipment is not inadvertently adjusted. The additional procedures that require equipment to be routinely calibrated, inspected, and checked, will also ensure that improperly calibrated equipment is not used. Therefore, FDA has deleted section 820.84(e). FDA notes that the failure to ensure against such event would be a violation of section 820.84, as well as section 820.70(g).

iii. Inspection and test status

1 Several comments on section 820.86, "Inspection and test status" stated that the requirements of the section were not flexible enough to allow identification of the inspection and test status of product by various means, given that the requirement is for the status to be "visible."

FDA agrees that the inspection and test status may be identified by any method that will achieve the result, which might include acceptable computerized identification. The section has been rewritten to reflect this intent, and is now consistent with ISO 9001:1994.

2 FDA has deleted section 820.86(b) which required that records identify those responsible for release of the product, because the agency believes that the records required by section 820.80(e) will necessarily identify those responsible for release of product.

<A NAME="pSubpart I">I. Nonconforming Product (Subpart I)</A>

1 FDA has rewritten section 820.90, "Nonconforming product" to utilize the term "product" throughout, as defined in section 820.3(s), for both shorthand purposes and consistency with ISO 9001:1994.

2 One comment suggested deleting the term "inadvertently" and adding the word "distributed" before "installed" in section 820.90(a).

FDA has deleted the term "inadvertently" because it believes that the control procedures should control the use or distribution of nonconforming product, whether "inadvertent" or otherwise. FDA also added the requirement that the procedures provide for the "evaluation" of nonconforming product because evaluation is key to protecting against recurring nonconformance. The addition is consistent with ISO 9001:1994.

3 One comment stated that the requirement that persons responsible for nonconforming product be "notified" should be deleted because it is overly burdensome and not needed in all cases.

FDA disagrees that this requirement should be deleted. Where some person or organization is responsible for nonconformances, they must be notified to ensure that future nonconformances are prevented.

4 FDA has rewritten section 820.90(b)(1), "Nonconformity review and disposition" to make clear that the section requires procedures that define the responsibility for review and authority for disposition of nonconforming product and set forth the review and disposition process. FDA believes that proper disposition of nonconforming product is essential for ensuring the safety and effectiveness of devices. Manufacturers have made determinations that nonconforming product may be used which have resulted in defective devices being distributed. Thus, although it may be appropriate at times to use nonconforming products, the disposition process must be adequately controlled.

Therefore, the revision requires that disposition and justification for concessions be documented. FDA believes that the justification should be based on scientific evidence and objective decision making, which a manufacturer should be prepared to provide upon request. Such concessions should be closely monitored and not become accepted practice.

This section is consistent with ISO 9001:1994, section 4.13.2.

5 Several comments were received on proposed section 820.90(b)(2). One comment stated that the requirement should allow for other types of disposition besides reprocessing. One comment suggested replacing the term "reinspection" with "evaluation," to allow for greater flexibility in verification methods. Many comments suggested that the requirement for identification of reprocessed product should be deleted because they believed it would cause the consumer to forego purchasing the product.

FDA agrees in part with the comments. FDA believes that the revised section 820.90(b)(1) clearly allows for other methods of disposition besides reprocessing. Section 820.90(b)(2), which governs reprocessing when it is chosen as a method of disposition, has been revised as requested to replace the requirement for "reinspection" with a requirement for "reevaluation." The requirement that reprocessing include "reevaluation" as compared to "reinspection" will allow manufacturers the flexibility to inspect or use other verification activities.

FDA has also, in response to the comments forecasting the negative impact reprocessing identification will have on sales, clarified its intent that such identification is required only during reprocessing.

6 Other minor changes made to the section include requiring that a determination as to the effect of reprocessing on a device be made, whether there is "repeated" reprocessing or not. FDA's intent is that such a determination be made with any reprocessing, given the potential harmful effect reprocessing could have on the product. The change harmonizes the section with ISO/DIS 13485. In addition, the sentence requiring a "complete reinspection" for reprocessed devices was deleted because the section already requires retesting and reevaluation of reprocessed product.

<A NAME="pSubpart J">J. Corrective and Preventive Action (Subpart J)</A>

1 A few comments suggested revising section 820.100(a), "Corrective and preventive action," to require procedures for implementing corrective and preventive action, consistent with ISO 9001. One comment stated that the procedures should provide for an initial halt of distribution of suspect products or tight control and action concerning products already distributed before taking the long term action listed in this section.

FDA agrees that it is essential that the manufacturer establish procedures for implementing corrective and preventive action and has revised section 820.100(a) accordingly. The procedures must include provisions for the remaining requirements in the section. These procedures must provide for control and action to be taken on devices distributed, and those not yet distributed, that are suspected of having potential nonconformities.

2 Other comments stated that the risk associated with a product failure should be commensurate with the degree of remedial action.

FDA agrees that the degree of corrective and preventive actions taken to eliminate or minimize the causes of actual or potential nonconformities must be appropriate to the magnitude of the problems and commensurate to the risks encountered. FDA cannot dictate in a regulation the degree of action that should be taken because each circumstance will be different, but FDA does expect the manufacturer to develop procedures for assessing the risk, the actions that need to be taken for different levels of risk, and how to correct or prevent the problem from recurring, depending on that risk assessment.

FDA emphasizes that any death, even if the manufacturer attributes it to user error, will be considered relevant by FDA and will have a high risk potentially associated with it. User error is still considered to be a

nonconformity because human factors and other similar tools should have been considered during the design phase of the device. FDA acknowledges that a manufacturer cannot possibly foresee every single potential misuse during the design of a device, but when the manufacturer becomes aware of that misuse, the corrective and preventive action requirements should be implemented to determine if redesign of the device or labeling changes may be necessary.

3 Several comments on section 820.100(a)(1) stated that requiring a manufacturer to analyze "all" processes, work operations, and other factors listed, is excessive and unrealistic. Some comments stated that there should not be a requirement to conduct analysis for "potential causes" of nonconformances. A few comments stated that the requirement that the analysis include "trend analysis" should be modified because it places unnecessary emphasis on only one statistical method or tool.

FDA agrees in part with the comments. It was not FDA's intent, for example, to require that processes unrelated to an existing nonconformity be analyzed, but to require that all those that could be at all related be analyzed. To prevent confusion, the word "all" has been deleted. The requirement is similar to that of ISO 9001:1994, section 4.14.3(a).

FDA has further revised the requirement to delete the reference to trend analysis in response to the comments. The provision now requires that "appropriate statistical methodology" be utilized. This revision is made because there may be other statistical tools available beyond what is now considered to be "trend analysis." FDA emphasizes that the appropriate statistical tools must be employed when utilizing statistical methodology. FDA has seen far too often the misuse of statistics by manufacturers in an effort to try to minimize a problem, instead of trying to address the actual problem. Such misuse of statistics would be a violation of this section.

FDA has retained the requirement for analysis to identify "potential causes of nonconforming product," however, because FDA believes this is an important aspect of preventive actions. FDA notes that ISO 9001:1994, section 4.14.1, specifically acknowledges that corrective and preventive actions are associated with actual and potential nonconformities.

4 Several comments stated that section 820.100(a)(2) was redundant with requirements in section 820.198, "Complaints."

FDA agrees in part with the comments and has written the section to require investigation of the cause of nonconformities relating to process, product, and the quality system, consistent with ISO 9001:1994, section 4.14.2(b). The requirement in this section is broader than the requirement for investigations under section 820.198, because it requires that nonconforming product discovered before or after distribution be investigated to the degree commensurate with the significance and risk of the nonconformity. At times a very in-depth investigation will be necessary, while at other times a simple investigation, followed by trend analysis or other appropriate tools will be acceptable. In addition, in contrast to section 820.198, the requirement in this section applies to process and quality system nonconformities, as well as product nonconformities. For example, if a molding process with its known capabilities has a normal 5 percent rejection rate and that rate rises to 10 percent, an investigation into the nonconformance of the process must be performed.

5 One comment stated that section 820.100(a)(3) should not require identification of action necessary to correct "other quality problems." Another stated that the section should be harmonized with ISO. One comment thought that the requirement should be to identify action to correct problems identified by "trend analysis."

FDA agrees that harmonization is important and has harmonized the terminology (and intent) of the section with ISO 9001:1994, sections 4.14.2(c) and 4.14.3(b). However, FDA disagrees that the section should not require identification of action necessary to correct "other quality problems" because the objective of section 820.100 is to correct and prevent poor practices, not simply bad product. Correction and prevention of unacceptable quality system practices should result in fewer nonconformities related to product. Therefore, this section addresses problems within the quality system itself. For example, it should identify and correct improper personnel training, the failure to follow procedures, and inadequate procedures, among other things.

In addition, FDA also disagrees with the suggestion to link the requirement in section 820.100(a)(3) to trend analysis, because the section requires the identification of the corrective or preventive action, not the problem or nonconformity. Further, FDA notes that the requirement for trend analysis to detect the quality problems has been modified in section 820.100(a)(1), in response to comments requesting its deletion.

6 FDA has revised section 820.100(a)(4) to reflect that preventive, as well as corrective, action must be verified or validated. The section is now consistent with ISO 9001:1994, sections 4.14.2(d) and 4.14.3(c). Two comments had stated that the definition of validation and verification cause confusion here, but FDA believes that these concerns should be resolved with the amended definitions under sections 820.3(cc) and (dd).

7 FDA has also revised section 820.100(a)(5) in the same manner, to relate the requirements to preventive action. This section is consistent with ISO 9001:1994, section 4.14.1, third paragraph.

8 One commentor suggested that section 820.100(a)(6) be revised to reflect that minor quality problems may not need to be disseminated to those directly responsible for ensuring quality and to be reviewed by management.

FDA agrees in part with the concern of this comment. The revision section requires that procedures provide for confirmation that relevant information on actions taken be distributed to management. This revision should redress the concern raised by the comment, in that only certain information would need to be directed to management. The manufacturer's procedures should clearly define what criteria will be followed to determine what information will be considered "relevant to the action taken" and why. FDA emphasizes that it is always management's responsibility to ensure that all nonconformity issues are handled appropriately. This section is now consistent with ISO 9001:1994 section 4.14.3(d).

9 Two comments stated that the records required under section 820.100(b) should be treated as part of the internal audit.

FDA disagrees with these comments because this information is directly relevant to the safety and effectiveness of finished medical devices. FDA has the authority to review such records and the obligation to do so to protect the public health. Comparable information and documentation is currently reviewed by the FDA under the requirements of the current device CGMP sections 820.20(a)(3) and (4) and 820.162. Manufacturers will be required to make this information readily available to an FDA investigator, so that the investigator may properly assess the manufacturer's compliance with these quality system requirements.

<A NAME="pSubpart K">K Handling, Storage, Distribution, and Installation (Subpart K)</A>

i. Handling

One comment on section 820.120, "Handling," suggested that the procedures be "designed to prevent," rather than be established to "ensure that," such problems delineated in the section do not occur. The commentor believed that the word

"prevent" would add clarity to the proposal, without compromising the meaning of the sentence. Another comment stated that the handling procedures should apply "prior to distribution," not during "any stage of handling."

FDA does not believe that the section, as written, is unclear. The procedures are expected to ensure that mixups, damage deterioration, or other adverse effects do not occur. FDA amended the requirement, however, to make it applicable "during handling." The requirement continues to apply to all stages of handling in which a manufacturer is involved, which may in some cases go beyond initial distribution.

ii. Storage

1 Two comments stated that section 820.122, "Storage" should be amended to be similar to ISO 9001, and that the rest of the requirements should be deleted and included in a guidance document. Another comment stated that restricting access to designated areas through the use of keys, bar code reader, among other means, should be sufficient to meet the intent of this requirement without the need for written procedures for authorizing receipt.

FDA agrees that the section could be more consistent with ISO 9001 and has revised the section to harmonize with ISO 9001:1994. FDA has not deleted the requirement for procedures to authorize receipt of product because the agency believes that strict control over product in storage areas and stock rooms results in decreased distribution of nonconforming product. Thus, even where locked storage rooms are utilized, the procedures should detail, among other things, who is permitted access and what steps should be followed prior to removal.

2 FDA has deleted the requirement that control numbers or identifications be legible and visible because it believes the requirement is contained in section 820.122(a), which requires the manufacturer to establish procedures to prevent mixups. To do this, a manufacturer must ensure that product can be properly identified.

iii. Distribution

1 A few comments on section 820.124(a), "Distribution" stated that there are times where, "first in, first out" inventory procedures may not be in the best interest of the customer. The comments said that especially when expiration dating is defined and labeled, a "first in, first out" system should not be required.

FDA agrees with the comments and has amended the requirement to state that the procedures must ensure that "expired devices or devices deteriorated beyond acceptable fitness for use" are not distributed.

2 Two comments under section 820.124(b) stated that class I devices should be exempt, or that the requirement should apply only to critical devices, because all device do not require a control number. Other comments stated that the term "consignee" should be defined, or the word "primary" should be added before "consignee" for clarity.

FDA agrees in part with the comments and has added the term "initial" before "consignee" to make clear that the requirement for maintaining distribution records extends on to the first consignee. FDA has retained the word "consignee" and notes that it is a person to whom the goods are delivered. FDA has also clarified that control numbers need only be maintained if required by section 820.65. FDA disagrees, however, that the requirement to maintain distribution records should not apply to Class I devices. The information required by this section is basic information needed for any class of product in order to conduct recalls or other corrective actions when necessary.

iv. Installation

1 Several comments received on section 820.126, "Installation" stated that not all devices require installation.

FDA agrees with the comments, but believes that it should be understood that the

installation requirements only apply to devices that are capable of being installed. However, to further clarify the regulation, FDA has made clear in the section that the requirement applies to "devices requiring installation."

2 A few comments raised the issue of applying the regulation requirements to third party installers.

FDA has rewritten this section consistent with the requirements for servicers under section 820.200, and has eliminated the distinction between installers authorized by the manufacturer and third parties. Under the revised provision, as in the proposal, manufacturers will be required to distribute the installation instructions and inspection procedures with the device, or make them otherwise available. This requirement is consistent with the current CGMP requirement in section 820.152.

As an addition to the installation requirements, however, the revised provision explicitly requires that the installation be performed according to the manufacturer's instructions, regardless of whether the installer is employed by or otherwise affiliated with the manufacturer. This requirement is implicit in the current (and proposed) requirement that the manufacturer distribute the installation instructions with the device, for use by third party installers.

The section requires records to be kept by whomever performs the installation, to establish that the installation was performed according to the procedures. Such records will be available for FDA inspection. FDA does not expect the manufacturer of the finished device to maintain records of installation performed by those installers not authorized by such manufacturer, but does expect the third party installer or the user of the device to maintain such records.

FDA believes that making these requirements explicit in the regulation is necessary to ensure that devices are safe and effective, and perform as intended, after installation. FDA notes that installers are currently considered to be manufacturers under the CGMP regulation and that their records are, and will continue to be, subject to FDA inspections where the agency deems it necessary to review such records.

<A NAME="pSubpart L">L. Packaging and Labeling Control (Subpart L)</A>

i. Device packaging

Two comments on section 820.160, "Device packaging" stated that the section should be changed to allow manufacturers to use third parties, if desired, for packaging.

FDA agrees with the comments and has changed the requirement accordingly.

ii. Device labeling

1 Several comments on section 820.162, "Device labeling" stated that the section should be deleted and placed in guidance because it is unnecessary and redundant with requirements under sections 820.80 and 820.86. A few comments stated that the section should be changed to be the same as that in the current device CGMP regulation, under sections 820.120 and 820.121.

FDA believes that the section, as written, is consistent with the current requirements. The sections are not redundant because section 820.162 relates specifically to labeling and its requirements are in addition to those in both sections 820.80 and 820.86. Further, FDA believes that the degree of detail in this section is necessary because these same requirements have been in the current regulation for 15 years, yet numerous recalls every year are the result of labeling errors or mixups. FDA therefore believes that more, not less, control is necessary.

2 A few comments stated that section 820.162(b), "Labeling inspections" should

allow automated readers to be used in place of a "designated individual(s)" to examine the labeling.

FDA disagrees with the comments because several recalls on labeling have been attributed to automated readers not catching errors. The requirement does not preclude manufacturers from using automated readers, where that process is followed by human oversight. A "designated individual" must examine, at a minimum, a representative sampling of all labels that have been checked by the automated readers. Further, automated readers are often programmed with only the base label and do not check the specifics such as controls numbers and expiration dates, among other things, that are distinct for each label, and the regulation requires that labeling be inspected for these items prior to release.

3 A few comments on proposed section 820.165, "Critical devices, labeling" stated that this section should be deleted to eliminate any distinctions between critical and noncritical devices.

FDA agrees and has deleted section 820.165, but has added a new section 820.162(e) to require that control numbers be on the device itself or its label where they are required by section 820.65.

<A NAME="pSubpart M">M. Records (Subpart M)</A>

i. General requirements

1 Several comments under section 820.180, "General requirements" suggested that FDA delete the requirement that records be stored to allow "rapid retrieval" because a reasonable timeframe should be allowed.

FDA has rearranged this section, and notes that records must be kept in a location that is "reasonably accessible" to both the manufacturer and FDA inspectors, and they must be made "readily available." FDA expects that such records will be made available during the course of an inspection. If the foreign manufacturer maintains records at remote locations, such records would be expected to be produced by the next working day or two, at the latest.

2 One comment stated that the wording of the section needed to be amended to allow records to be located in different places, especially for foreign manufacturers and distributors.

FDA has clarified that records can be kept at other than the inspected establishment, provided that they are made "readily available" for review and copying. This should provide foreign manufacturers and distributors the necessary flexibility.

3 One comment stated that wherever the word "all" appeared in the requirements, FDA should delete it. In response, FDA notes that where a requirement exists for ensuring that records are maintained in a certain fashion, a manufacturer must keep all records subject to the regulation in that manner. Manufacturers cannot pick and choose which records they will, for instance, make legible. The revised section makes clear that it is "all records required" by the regulation to which the section's requirements pertain.

4 A few comments on section 820.180(b), "Record retention period" stated that the section should be amended because all quality records may not be tied to a specific device; therefore, such quality records may not need to be maintained over the lifetime of a device. A few comments stated that the retention period requirement is unclear, or that the period should be left to the manufacturer to define.

FDA believes that all records should be retained for a period equivalent to the design and expected life of the device, but in no case less than 2 years, whether the record specifically pertains to a particular device or not. The requirement is amended to make clear that all records, including quality records, are subject to the requirement. FDA believes this is necessary because manufacturers need all such

records when performing any type of investigation. For example, it may be very important to access the wording of a complaint handling procedure at the time a particular complaint came in when investigating a trend or a problem that extends to several products or over an extended period of time. Further, FDA does not believe that allowing the manufacturer to define the retention period will serve the public's best interest with regard to safety concerns and hazard analysis.

5 One comment suggested the deletion of the requirements related to photocopying records in section 820.180(b) because it is technology that is not necessarily being used.

In response, FDA has deleted the last two sentences. The agency believes that this requirement is outdated and does not necessarily reflect the technology being utilized today. Further, the general requirement in section 820.180 to make the records readily available for inspection and copying by FDA would mandate that such equipment be available for an inspector's use.

6 One comment stated that all quality audit reports should be subjected to FDA review and public disclosure.

FDA disagrees with this comment for the reasons given in the preamble of the original CGMP regulation, published in the Federal Register on July 21, 1978 (43 FR 31508), and believes that the disclosure of the audit reports themselves would be counterproductive to the intent of the quality system. FDA has added section 820.180(c), "Exceptions" to address which records FDA, as a matter of administrative policy, will not request to review and copy during a routine inspection; such records include supplier audit reports where used to comply with section 820.50(a). FDA may request an employee in management with executive responsibility to certify in writing that the management reviews, quality audits, and supplier audits (where conducted) have been performed, among other things. FDA may also seek production of these reports in litigation under applicable procedural rules or by inspection warrant where access to the records is authorized by statute.

Again, FDA emphasizes that its policy of refraining from reviewing these reports extends only to the specific reports, not to the procedures required by the sections or to any other quality assurance records. Such documents will be subject to review and copying.

ii. Device master record (DMR)

1 One comment on section 820.181, "Device master record" stated that the requirement for a "qualified" individual to prepare the DMR should be deleted because it is unclear.

FDA has not deleted the requirement for the DMR to be prepared, dated, and approved by a qualified individual because the agency believes this is necessary to assure consistency and continuity within the DMR. The section is consistent with the current device CGMP section 820.181.

2 One comment on section 820.181(a) stated that "software design specifications" should not be included in the DMR because these documents will be located in the design history file (DHF). Another comment requested that the requirement that the DMR contain "software source code" information be amended because source code for commercialized software will not be available to the device manufacturers.

FDA agrees with the comments and has amended the requirement to require that "software specifications," and "software source code" for customized software, be included in the DMR.

3 One comment on section 820.181(c) stated that the DMR should not contain quality system documents, but rather the quality control documents related to the

specific device. Three comments stated that validation and verification information should belong in the design history file, not the DMR.

FDA agrees in part with the comments and has revised the section to clarify that the quality records required in the DMR relate to the specific current design, not the more general requirements of the quality system, which are addressed under new section 820.186. However, the comments are incorrect that all validation and verification information is related solely to design. There are requirements for validation and verification pertaining to device processing that may better be kept in the DMR instead of the DHF.

4 FDA notes that the regulation contains a few requirements which apply "where appropriate" or "at appropriate stages." FDA emphasizes that the procedures that the manufacturer places in the DMR must clearly define the requirements the manufacturer is following. For example, the design review procedures established under section 820.30(e) must clearly define at which stages the review will occur. The manufacturer will have failed to comply with the requirements of the section if the procedures state that the review will occur at "appropriate stages."

The same principle applies for every section of this regulation, which is written to be flexible enough to cover the manufacture of all types of devices. Manufacturers must adopt a quality system appropriate to their specific products and processes. In establishing these procedures, FDA will expect manufacturers to be able to provide justifications for the decisions reached.

iii. Device history record

1 One comment stated that labeling should not be required in the DHR because it is already required in the DMR.

FDA agrees that it may not be necessary to include all labeling actually used in the DHR, and understands that this requirement may be burdensome. However, FDA continues to believe, as it explained in the preamble to proposed regulation published in the Federal Register on November 23, 1993, (58 FR 61968), that increased control over labeling is necessary due to the many labeling errors resulting in recalls. Therefore, FDA has retained a requirement related to labeling in the DHF, but revised it to make it less burdensome. The requirement is now similar to that contained in the current device CGMP regulation, section 820.185. FDA believes that requiring the DHF to identify the specific label, labeling, and control number used for each production unit, coupled with the labeling controls in section 820.162, should help to ensure that proper labeling is used and, hopefully, decrease the number of recalls due to improper labeling.

2 FDA has deleted the requirement for the DHR to be "readily accessible and maintained by a designated individual(s)" because it believes that the objective of that requirement is met through sections 820.40(a), "Document controls" and 820.180, "Records, general requirements."

FDA has also added "device identification" to the requirement under section 820.184(d) because it believes that where any identification or control number is used, it should be documented in the DHR to facilitate investigations, as well as corrective and preventive actions. FDA notes that this provision does not add any requirement for identification or traceability not already expressed in sections 820.60 and 820.65.

iv. Quality system records

Several comments stated that the regulation should more closely harmonize with ISO 9001:1994. A few comments stated that the regulation should include the requirements for a quality manual. One comment stated that general quality system procedures and instructions should not be required in the DMR because the DMR is device specific, and many quality system procedures are not tied to a particular device.

FDA agrees in part with these comments and has developed a new section 820.186, "Quality system records." This section separates the quality system records from the device specific records. The requirements under section 820.186(a) incorporate the principles of quality planning, and sections 820.186(b) and (c) incorporate the principles of a quality policy and certain aspects of a quality manual. The requirement under section 820.186(d) for an outline is found in ISO 9001:1994, section 4.2.1. FDA believes that outlining the structure of the documentation used in the quality system is a very beneficial exercise and, at times, may be critical to the effective operation of the quality system. FDA recognizes, however, that it may not be necessary to create such an outline in all cases. For example, it may not be necessary for smaller manufacturers and manufacturers of less complicated devices. Thus, the outline is only required where appropriate.

v. Complaint files

1 Two comments on section 820.198, "Complaint files," stated that the requirements were very detailed and that much of the language should be placed in a guidance document.

FDA disagrees with the comments. These requirements are essentially the same as the CGMP requirements under current section 820.198, and 15 years of experience with these requirements shows that many manufacturers still do not understand and properly handle complaints. Therefore, FDA believes that the amount of detail in this section is appropriate and necessary. In an effort to make the requirements more clear, however, the section has been reorganized to better illustrate how complaint information should be handled.

2 A few comments on section 820.198(a) stated that the section should allow for more than one "formally designated unit" to handle complaints.

FDA disagrees with these comments. While large corporations may have different complaint handling units for different product lines or different manufacturing establishments, it is very important that only one formally designated complaint handling unit be responsible for the overall complaint handling to ensure uniformity in the application of the complaint procedures. If multiple designated units are set up at each servicing facility, there will be multiple interpretations on handling, evaluating, categorizing (when accomplished), investigations, and follow-ups. That would be unacceptable. Therefore, the manufacturer should establish in its procedures which one group or unit is ultimately responsible for coordinating all complaint handling functions.

3 Several comments on proposed section 820.198(b) stated that the evaluation of complaints pertaining to death, injury, or hazard to health should be removed from this section because it is redundant with the Medical Device Reporting regulation.

FDA disagrees that the requirements are redundant, but believes that they expressly state what is expected in the handling of this type of complaint information. The requirements have been moved to a separate section, section 820.198(d).

4 Several other comments on section 820.198(b) (now section 820.198(d)) stated that complaints pertaining to death, injury, or hazard to health need not be maintained separately, as long as they are identified.

FDA agrees and has revised the section to permit such complaints to be "clearly and visibly identified as" pertaining to death, injury, or hazard to health. This will permit a manufacturer flexibility in choosing a means of ensuring that these types of complaints are immediately recognized and "segregated" for the purpose of prioritizing and meeting other requirements.

5 A few comments on sections 820.198(c) and (d) stated that FDA should make clear that some of the requirements will not always be applicable.

For example, the comments state that a record of corrective action cannot be made if it is not required to be, and is not, taken.

As noted in a prior response, FDA believes that it should be understood that the regulation requires documentation of corrective action, for example, where corrective action is not necessary and is not taken, it cannot be documented. However, the section was revised to make that clear. As stated in the preamble to the proposal in the Federal Register of November 23, 1993, (58 FR 61968), the manufacturer's procedures should clearly identify when corrective action, and all other requirements, will and will not be taken.

In addition, FDA combined provisions in sections 820.198(c) - (e) to eliminate redundancy and added the requirement that the records include any device identification, as well as control number used, to facilitate corrective and preventive actions.

6 FDA deleted the requirements originally stated in section 820.198(f) in response to comments because it agrees that it is not necessary to repeat the requirements of the Medical Device Reporting (MDR) regulation in the Quality System regulation. Section 820.198(a) requires all complaints to be evaluated to determine whether the complaint is subject to the requirements of the MDR regulation under part 803. When it is, the requirements of that part must be followed.

7 A few comments on section 820.198(g), now section 820.198(e), stated that duplicate records are not needed in this age of computer systems, and that the requirement as written would be counterproductive.

FDA agrees with the comments and has rewritten the section to allow the complaints and record of investigations to be concurrently maintained at the location of the formally designated complaint unit and the actual manufacturing site, where these locations are distinct. Where this is done, the procedures must ensure that the actual manufacturer is alerted to the receipt of complaints.

8 Several comments on section 820.198(h), now section 820.198(f), stated that the requirement is unnecessary given that FDA can inspect a foreign manufacturer that imports devices and is burdensome.

FDA has revised the section to permit the records to be concurrently maintained, which should alleviate a great deal of the perceived burden. However, the agency must have access to these records here in the United States.

9 Several comments on sections 820.198(i) and (j) stated that the requirements should be deleted because they are redundant with the MDR requirements in part 803.

FDA disagrees that all of the requirements in these sections are redundant. The requirement that procedures ensure that complaints are processed uniformly and timely, and evaluated to determine whether they are reportable under Part 803, has been moved up into section 820.198(a). These are basic requirements for complaint handling. If the complaint is determined to be of the type subject to part 803, those requirements apply. They are not repeated in this regulation. FDA has deleted section 820.198(j).

<A NAME="pSubpart N">N. Servicing (Subpart N)</A>

1 Several comments on section 820.200, "Servicing" suggested that third party servicers should be held responsible under the regulation for actions taken on devices.

FDA agrees for the reasons that will be discussed below, and has revised this section accordingly. The provision now requires that the original manufacturer of the finished device (which would include the refurbisher of a refurbished device) distribute, or otherwise make available, the device's safety and performance

specifications to allow for proper servicing. These performance specifications must include the device's end-of-life date or period. Without such instructions and specifications, a servicer simply cannot properly service a device.

Servicers who are not under the manufacturer's control, as well as those who are, would be required to service the device according to the instructions, and to maintain records to demonstrate that the device has been so serviced. These records are necessary to demonstrate that servicing was performed in accordance with any instructions and procedures established by the original manufacturer, and thus to protect the public health by ensuring that the device performs as intended. The third party servicer's records would be subject to FDA review.

Finally, the third party servicer is required to provide copies of the service reports to the original manufacturer (including the refurbisher) so that such reports may be analyzed according to appropriate statistical methodology. FDA firmly believes that the original manufacturer must analyze all service reports to properly assess whether there is an early wear out failure for a particular component or subassembly, to detect any misuse by users, and to detect any design flaws, among other things.

2 Other comments stated that it is impractical to return a used device to its original specifications because a certain amount of wear and tear should be expected, without detriment to the safety and effectiveness of the device.

FDA agrees and revised the requirement in section 820.200 to provide that the servicing must ensure that the device will meet specified requirements for the device's intended use. FDA is aware that with use and age, a device may be serviced to function as intended, but may not meet original specifications.

3 Several comments on section 820.200(a) stated that the term "records" should be replaced by "reports," to be consistent with ISO 9001.

FDA agrees with the comments and has changed sections 820.200(a) and (b) accordingly. FDA has also added the requirement for recording any device identification, as well as control number, where used because FDA believes such documentation in the service report will facilitate investigations, as well as corrective and preventive actions. This additional documentation provision does not add any requirement for identification or traceability not already expressed in sections 820.60 and 820.65.

4 A few comments on section 820.200(b), "Service report evaluation" questioned if full corrective action was necessary for every service report and whether service calls need to be handled as complaints only when there is a death, injury, or hazard to safety.

FDA has amended this section to clarify the agency's intent and to use terms consistent with those used in section 820.198. Full corrective action may not be required for every service report, but the corrective and preventive action requirements are initiated with each report, and the manufacturer must analyze the reports accordingly to "appropriate statistical methodology." If the analysis indicates that the risk is high, or that the frequency is higher than expected, the remainder of the corrective and preventive action elements are applicable, in accordance with the corrective and preventive action procedures established under section 820.100.

The last sentence in section 820.200(b) provides that when a service report involves a death, injury, or hazard to safety, it is automatically considered by FDA to be a complaint, which must be handled according to section 820.198. FDA emphasizes that this provision does not limit "complaints" to only those involving deaths, injuries, or hazard to safety.

<A NAME="pSubpart O">O. Statistical Techniques (Subpart O)</A>

1 FDA amended section 820.250(a) to be consistent with the requirements in ISO 9001:1994, section 4.20.

2 Several comments on section 820.250(b) stated that the requirement as written seems to require the use of sampling plans, and that every manufacturer does not necessarily use sampling plans. Another comment stated that sampling plans are not often used during reviews of nonconformities, quality audits, or complaints, and that these examples should, therefore, be deleted.

FDA's intent was not to require the use of sampling plans, but to require that where they were used, they would be written and valid. The section was revised to make that clear. Sampling plans are not always required, but any time the sampling plans are used, they must be based on a valid statistical rationale. Further, FDA acknowledges that the most common use of sampling plans is during receiving acceptance, and has deleted the examples.

ENVIRONMENTAL IMPACT

The agency has determined under 21 CFR sections 25.24(a)(8) and (e)(2) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

ECONOMIC IMPACT

FDA has examined the costs and benefits of the proposed rule of November 23, 1993, to revise the CGMP regulation covering medical devices (21 CFR part 820) in accordance with Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354).

The detailed data for this analysis were developed by ERG, under contract to FDA, and the full report, "Economic Analysis of Proposed Revisions to the Good Manufacturing Practices Regulation for Medical Devices," is on file at the Dockets Management Branch (address above) and was discussed in the preamble of the November 23, 1993, proposed regulation. FDA has determined that it would not be cost beneficial or meaningful to contract for an amended economic impact study at this time because many issues are currently deemed to be open for comment and final decision pending the additional comment period and the GMP Advisory Committee meeting. For example, the decision on whether certain components suppliers, refurbishers, and third party servicers are subject to this regulation will influence the economic impact of the final regulation. In addition, the application of the design control requirements on investigational devices may also affect the economic impact of the regulation.

Without taking these issues into account, the agency believes that the changes from the proposal to the Working Draft will not increase the estimates in the 1993 report and may possibly lesson the economic impact, given that FDA has deleted many of the more prescriptive requirements and more closely harmonized with the latest versions of the ISO standards.

Only a small portion of the comments received addressed the economic impact. Five major points emerged from these comments.

1 Many comments generally stated that the economic impact report significantly underestimated the cost of compliance with the proposed regulation. The comments seemed to base this conclusion on an assumption that most manufacturers lack of any system controls or design capabilities.

FDA does not agree with this impression. The agency believes that no manufacturer should be starting from zero compliance, and that most manufacturers have systems of control even in the few new areas addressed by the regulation, or they would not be in business. Further, the economic impact may be even less because the contractor assumed some existing compliance and regulatory capability, but not full compliance.

FDA acknowledges a possible underestimate in the training costs. The contractor assumed a one time bolus of training for RA, QA, and designers specifically, and

did not factor in continuing training costs. FDA believes that this underestimate is minimal, however, because all manufacturers are already required to have a continuing training program and it is only considered to be an underestimate if it is assumed that this continual training will be conducted by consultants. This is generally not the case, although some commentors believed that manufacturers may lack in-house expertise and therefore be required to employ consultants in this capacity.

2 Several comments stated that the economic impact would be much greater for small manufacturers and that the proposal as written may force many small manufacturers out of business.

FDA acknowledges that there most likely would be a greater impact from small manufacturers, especially if these small manufacturers have no system controls on their design process. FDA, through its Division of Small Manufacturers Assistance (DSMA), has a number of programs designed to assist small businesses. DSMA provides guidance materials, regional seminars, and technical assistance that can help small businesses with their compliance activities. Further, FDA has looked at some specific small start-up biotechnology firms, who chose to implement design controls similar to those required in the regulation. FDA found that the time to distribution was longer and more expensive with the implementation of design controls, but that over a period of approximately two years, the implementation saved money in fewer recalls, and less redesigning, retrofitting, and retraining. Added to this cost/benefit ratio is the obvious benefit of increased protection of the public health.

3 Some commentors stated that the general benefits do not offset the costs. The comments further stated that the proposed regulation would stifle innovation and slow product development.

FDA disagrees. Many great quality experts such as Juran, Deming, and Taguchi have taught the cost benefits of design control for years. Actual proof of such cost benefits can be seen in the U.S. automotive industry over the past few years. Design controls do not and are not meant to stifle innovation. Design controls simply give the design process a logical framework to progress in, where the system is set up to eliminate problems at an earlier stage thereby inherently introducing a higher quality product. Thus, FDA agrees, as stated in the previous response, that design controls may slow product development, but maintains that the cost is lower in the long run.

4 A few comments stated that the cost benefits of harmonization would be greater if the proposed regulation was even more closely harmonized with the current ISO standards.

FDA agrees and has made a very concerted effort to more closely harmonize with the current versions of the ISO standards, as evidenced throughout this preamble.

5 Some commentors expressed great concern about the economic impact of component manufacturers being required to comply with the revised regulation.

As discussed above, FDA agrees that application of this regulation to component manufacturers will influence the economic impact of the final regulation. In this extended comment period, FDA is seeking information about whether it is appropriate to apply these requirements to manufacturers of components or parts intended specifically for use as part of a finished medical device.

PAPERWORK REDUCTION ACT OF 1990

As stated for the Economic Impact, FDA does not believe it to be advantageous or beneficial to conduct an amended study on the paperwork reduction at this time because changes may result depending on the assumptions of this regulation related to component manufacturers, refurbishers, and third party servicers, as well as investigational devices. Putting these issues aside, FDA believes that the estimate would be similar or reduced

from the proposal due to the many changes made in response to comments to more closely harmonize with the current ISO standards.

Organizations and individuals desiring to submit comments for consideration by OMB on these information collection requirements should direct them to FDA's Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, Office of Management and Budget, rm. 3001, New Executive Office Bldg., 725 17th St. NW., Washington, DC 20503, Attn: Desk Officer for FDA.

REFERENCES

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

ISO 9001:1994 "Quality Systems - Model for Quality Assurance in Design, Development, Production, Installation, and Servicing."

ISO working draft revision of ISO/DIS 13485 "Quality Systems - Medical Devices - Supplementary Requirements to ISO 9001."

Federal Register Notice of November 30, 1990, (55 FR 49644), entitled "Medical Devices; Current good Manufacturing Practices (CGMP) Regulations Document; Suggested Changes; Availability."

Federal Register Notice of November 23, 1993, (55 FR 61952) entitled "Medical Devices; Current Good Manufacturing Practice (CGMP) Regulations; Proposed Revisions; Request for Comments."

European Norm (EN) standard EN 46001 "Quality Systems - Medical Devices - Particular Requirements for the Application of EN 29001."

Copies of slides from workshops and seminars discussing the revision of the CGMP regulation and FDA's intent.

"Guideline on General Principles of Process Validation," FDA, Center for Drugs and Biologics, and Center for Devices and Radiological Health, Rockville, MD 20857, May 1987.

<A NAME="183">WORKING DRAFT OF THE CGMP FINAL RULE - REGULATION</A>

<A NAME="rSubpart A">Subpart A - General Provisions</A>

820.1 Scope.

(a) Applicability.

(1) Current good manufacturing practice (CGMP) requirements are set forth in this quality system regulation. The requirements in this part govern the methods used in, and the facilities and controls used for, the design, purchasing, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use. The regulations in this part are intended to ensure that finished devices will be safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act (the act). This part establishes basic requirements applicable to manufacturers of finished medical devices. With respect to class I devices, design controls apply only to those devices listed in 820.30(a)(2). The regulations in this part do not apply to manufacturers of components or parts of finished devices when such components or parts are not intended specifically for use as part of a medical device, but such manufacturers are encouraged to use appropriate provisions of this regulation as guidelines. Manufacturers of human blood and blood components are not subject to this part, but are subject to part 606 of this chapter.

(2) The provisions of this part shall be applicable to any finished device and component described above, as defined in this part, intended for human use, that is manufactured, imported, or offered for import in any State or Territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

(b) Limitations. The quality system regulation in this part supplements regulations in other parts of this chapter except where explicitly stated otherwise. In the event that it is impossible to comply with all applicable regulations, both in this part and in other parts of this chapter, the regulations specifically applicable to the device in question shall supersede any other regulations.

(c) Authority. Part 820 is established and promulgated under authority of sections 501, 502, 510, 513, 514, 515, 518, 519, 520, 522, 701, 704, 801, and 803 of the act (21 U.S.C. 351, 352, 360, 360c, 360d, 360e, 360h, 360i, 360j, 360l, 371, 374, 381, and 383). The failure to comply with any applicable provision in this part renders the device adulterated under section 501(h) of the act. Such a device, as well as any person responsible for the failure to comply, is subject to regulatory action under sections 301, 302, 303, 304, and 801 of the act.

(d) Foreign manufacturers. If a manufacturer who offers devices for import into the United States refuses to permit or allow the completion of an FDA inspection of the foreign facility for the purpose of determining compliance with this part, it shall appear for purposes of section 801(a) of the act, that the methods used in, and the facilities and controls used for, the design, purchasing, manufacture, packaging, labeling, storage, installation, or servicing of any devices produced at such facility that are offered for import into the United States do not conform to the requirements of section 520(f) of the act and this part and that the devices manufactured at that facility are adulterated under section 501(h) of the act.

(e) Exemptions or variances. (1) Any person who wishes to petition for an exemption or variance from any device quality system requirement is subject to the requirements of section 520(f)(2) of the act. Petitions for an exemption or variance shall be submitted according to the procedures set forth in 10.30 of this chapter, the Food and Drug Administration's administrative procedures. Guidance is available from the Center for Devices and Radiological Health, Division of Small Manufacturers Assistance, Regulatory Assistance Branch (HFZ-220), 1350 Piccard Drive Rockville, MD 20850, telephone 1-800-638-2041, or 1-301-443-6597, FAX 301-443-8818.

(2) FDA may initiate and grant a variance from any device quality system requirement where the agency determines that such variance is in the best interest of the public health. Such variance will remain in effect only so long as there remains a public need for the device and the device would not likely be made sufficiently available without the variance.

820.3 Definitions.

(a) Act means the Federal Food, Drug, and Cosmetic Act, as amended (secs.

201-903, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321-394)). All definitions in section 201 of the act shall apply to these regulations.

(b) Complaint means any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device.

(c) Component means any raw material, substance, piece, part, software, firmware, packaging, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.

(d) Control number means any distinctive symbols, such as a distinctive combination of letters or numbers, or both, from which the complete history of the purchasing, manufacturing, packaging, labeling, and distribution of a unit, lot, or batch of finished devices can be determined.

(e) Design History File means a compilation of records which describe the complete design history of a finished device.

(f) Design input means the physical and performance requirements of a device that are used as a basis for device design.

(g) Design output means the results of a design effort at each design phase and at the end of the total design effort. The total finished design output consists of the device, its packaging and labeling, the associated specifications and drawings, and the production and quality assurance specifications and procedures. The finished design output will be the basis for the device master record.

(h) Design review means a documented, comprehensive, systematic examination of a design to evaluate the adequacy of the design requirements, to evaluate the capability of the design to meet these requirements, and to identify problems and propose the development of solutions.

(i) Device history record means a compilation of records containing the complete production history of a finished device.

(j) Device master record (DMR) means a compilation of records containing all the procedures and specifications related to a specific finished device, as required by this part.

(k) End of life means an established time to failure period, determined by the original device manufacturer, based upon reliability data and analysis to characterize nonrepairable product.

(l) Establish means define, document (written or electronic), and implement.

(m) Finished device means any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labeled, or sterilized.

(n) Lot or batch means one or more components or finished devices that consist of a single type, model, class, size, composition, and software version that are manufactured under essentially the same conditions and that are intended to have uniform characteristics and quality within specified limits.

(o) Management with executive responsibility means those senior employees of a manufacturer who have the authority to establish or make changes to the manufacturer's quality policy and quality system.

(p) Manufacturer means any person who designs, manufactures, fabricates, assembles, or processes a finished device or components or parts intended specifically for use as part of a finished medical device, and includes contract sterilizers, specification developers, repackers, relabelers, refurbishers, servicers, and initial distributors of imported devices.

(q) Manufacturing material means any material or substance used in, or used to facilitate, a manufacturing process, or a naturally occurring substance, that is not intended by the manufacturer to be included in the finished device, including cleaning agents, mold-release agents, lubricating oils, and sterilant residues, or other byproducts of the manufacturing process.

(r) Nonconformity means the nonfulfillment of a specified requirement.

(s) Product means components, manufacturing materials, in-process devices, finished devices, and returned devices.

(t) Quality means the totality of features and characteristics that bear on the ability of a device to satisfy fitness-for-use, including safety and performance.

(u) Quality audit means an established systematic, independent, examination of a manufacturer's quality system that is performed at defined intervals and at sufficient frequency to ensure that both quality system activities and the results of such activities comply with specified quality system procedures, that these procedures are implemented effectively, and that these procedures are suitable to achieve quality system objectives.

(v) Quality policy means the overall quality intentions and direction of an organization with respect to quality, as formally expressed by management with executive responsibility.

(w) Quality system means the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

(x) Record means any written or electronic document, including specifications, procedures, protocols, standards, methods, instructions, plans, files, forms, notes, reviews, analyses, data, and reports.

(y) Refurbisher means any person who processes, conditions, renovates, or restores a finished device which has been previously distributed, and has reached its established end-of-life or is considered to be nonrepairable.

(z) Reprocessing means all or part of a manufacturing operation which is intended to correct nonconformance in a component or finished device before distribution.

(aa) Servicing means maintenance or repair of a finished device after distribution for purposes of returning it to its safety and performance specifications established by the original finished device manufacturer and to meet its original intended use, prior to the device's established end-of-life or before it is considered to be nonrepairable.

(bb) Specification means any requirement with which a product, process, service, or other activity must conform.

(cc) Validation means establishing and documenting evidence which provides a high degree of assurance that a process will consistently produce a result or product meeting its predetermined specifications.

(dd) Verification means confirmation by examination and provision of objective evidence that specified requirements related to a product or process have been met.

820.5 Quality system.

Each manufacturer shall establish and maintain a quality system that is appropriate to the specific medical device manufactured and meets the requirements of this part. Each manufacturer shall:

(a) Establish effective quality system instructions and procedures in accordance with the requirements of this part; and,

(b) Maintain the established quality system instructions and procedures effectively.

<A NAME="rSubpart B">Subpart B - Quality System Requirements</A>

820.20 Management responsibility.

(a) Quality policy. Management with executive responsibility shall establish its policy and objectives for, and commitment to, quality. Management with executive responsibility shall ensure that the quality policy is understood, implemented, and maintained at all levels of the organization.

(b) Organization. Each manufacturer shall establish and maintain an adequate organizational structure to ensure that devices are produced in accordance with the requirements of this part.

(1) Responsibility and authority. Each manufacturer shall establish the appropriate responsibility, authority, and interrelation of all personnel who manage, perform, and verify work affecting quality, and provide the independence and authority necessary to perform these tasks.

(2) Resources. Each manufacturer shall provide adequate resources, including the assignment of trained personnel, for management, performance of work, and verification activities, including internal quality audits, to carry out the requirements of this part.

(3) Management representative. Management with executive responsibility shall appoint, and document such appointment of, a member of management who, irrespective of other responsibilities, shall have established authority over and responsibility for:

(i) Ensuring that quality system requirements are established and maintained in accordance with this part; and

(ii) Reporting on the performance of the quality system to management with executive responsibility for review.

(c) Management review. Management with executive responsibility shall review the suitability and effectiveness of the quality system at defined intervals and at sufficient frequency according to established procedures to ensure that the quality system satisfies the requirements of this part and the manufacturer's established quality policy and objectives. The results of quality system reviews shall be documented.

820.22 Quality audit.

Each manufacturer shall conduct quality audits to verify that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system. Quality audits shall be conducted in accordance with established audit procedures by individuals who do not have direct responsibility for the matters being audited. A report of the results of each quality audit, and reaudit(s) where taken, shall be made and such reports shall be reviewed by management having responsibility for the matters audited. Follow-up corrective action, including a reaudit of deficient matters, shall be taken when necessary. The dates on which the audit and reaudit were performed shall be documented.

820.25 Personnel.

(a) General. Each manufacturer shall employ sufficient personnel with the necessary education, background, training, and experience to ensure that all activities required by this part are correctly performed.

(b) Training. Each manufacturer shall ensure that all personnel are trained to adequately perform their assigned responsibilities. Training shall be conducted in accordance with established procedures to ensure that employees have a thorough understanding of their current job functions and with the CGMP requirements applicable to their job functions. As part of their training, employees shall be made aware of device defects which may occur from the improper performance of their specific jobs. Personnel who perform verification activities shall be made aware of defects and errors that may be encountered as part of their verification functions. Employee training shall be documented.

<A NAME="rSubpart C">Subpart C--Design Controls</A>

820.30 Design controls.

(a) General. (1) Each manufacturer of any class III, or class II device, and the class I devices listed in paragraph (a)(2) of this section, shall establish and maintain procedures to control and verify the design of the device in order to ensure that specified design requirements are met.

(2) The following class I devices are subject to design controls:

(i) Devices automated with computer software; and

(ii) The devices listed in the chart below.

Section	Device
868.6810	Catheter, Tracheobronchial Suction
878.4460	Glove, Surgeon's
880.6760	Restraint, Protective
892.5650	System, Applicator, Radionuclide, Manual
892.5740	Source, Radionuclide Teletherapy

(b) Design and development planning. Each manufacturer shall establish and maintain plans that describe or reference the design and development activities and define responsibility for the implementation. The design and development activities shall be

assigned. The plan shall include and describe the interfaces with different groups or activities. The plans shall be reviewed, updated, and approved as design and development evolves.

(c) Design input. Each manufacturer shall establish and maintain procedures to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient. The design input requirements shall be documented and shall be reviewed and approved by a designated individual(s). The approval including the date and signature of the individual(s) approving the requirements, shall be documented.

(d) Design output. Each manufacturer shall establish and maintain procedures for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements. Design output procedures shall ensure that design output meets the design input requirements. Design output procedures shall contain or make reference to acceptance criteria and shall ensure that those design outputs that are essential for the proper functioning are identified. Design output documents shall be reviewed and approved before release. The approval, including the approval date and the signature of the individual(s) approving release, shall be documented.

(e) Design review. Each manufacturer shall establish and maintain procedures to ensure that formal documented reviews of the design results are planned and conducted at appropriate stages of the device's design development. Each manufacturer shall assign an individual(s), who does not have direct responsibility for the design development, to participate in the design reviews. The procedures shall ensure that participants at each design review include representatives of all functions concerned with the design stage being reviewed, as well as specialists where appropriate. The results of a design review shall be documented in the design history file.

(f) Design verification and validation. Each manufacturer shall establish and maintain procedures for verifying and validating the device design. Design verification shall confirm that design output meets the design input requirements. Design validation shall ensure that devices conform to defined user needs and intended uses. Design validation shall be performed under defined operating conditions and on the initial production units, lots, or batches. Design validation, and verification where appropriate, shall include testing of production units under actual or simulated use conditions before distribution. The results of the design verification and validation, including identification of the design, method(s), the date, and the individual(s) performing the verification and validation shall be documented in the design history file. Design verification and validation shall include software validation, and an analysis of available information to identify potential sources of harm and estimate their probable rate of occurrence and degree of severity.

(g) Design transfer. Each manufacturer shall establish and maintain procedures to ensure that the design basis for a device and its components is correctly translated into production specifications.

(h) Design changes. Each manufacturer shall establish and maintain procedures for the identification, documentation, validation, or verification where appropriate, review, and approval of design changes.

(i) Design history file. Each manufacturer shall establish and maintain a design history file for each design. The design history file shall contain or reference all records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of this part.

<A NAME="rSubpart D">Subpart D--Document Controls</A>

820.40 Document controls.

Each manufacturer shall establish and maintain procedures to control all documents that are required to be established, maintained, and removed under this part. The procedures shall provide for the following:

(a) Document approval and distribution. Each manufacturer shall designate an individual(s) to review and approve all documents established to meet the requirements of this part for adequacy prior to issuance. The approval, including the approval date and signature of the individual(s) approving the document, shall be documented. Documents established to meet the requirements of this part shall be available at all locations for which they are designated, used, or otherwise necessary, and all obsolete documents shall be promptly removed from all points of use or otherwise prevented from unintended use.

(b) Document changes. Changes to documents shall be reviewed and approved by individuals in the same functions/organizations that performed the original review and approval, unless specifically designated otherwise. Approved changes shall be communicated to the appropriate personnel in a timely manner. Each manufacturer shall maintain records of changes to documents. Change records shall include a description of the change, identification of the affected documents, the signature of the approving individual(s), the approval date, and when the change becomes effective.

<A NAME="rSubpart E">Subpart E--Purchasing Controls</A>

820.50 Purchasing controls.

Each manufacturer shall establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements.

(a) Evaluation of suppliers, contractors, and consultants. Each manufacturer shall establish and maintain evaluation criteria for suppliers, contractors, and consultants that specify the requirements, including quality requirements, that must be met. Each manufacturer shall:

(1) Evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements. Records of the evaluation results shall be maintained.

(2) Define the type and extent of control to be exercised over the product, services, suppliers, contractors, and consultants based on the evaluation results.

(3) Establish and maintain records of acceptable suppliers, contractors, and consultants.

(b) Purchasing data. Each manufacturer shall establish and maintain purchasing data that clearly describe or reference the specified requirements, including quality requirements, for purchased product and services. Purchasing documents shall include, where possible, an agreement that the suppliers and contractors agree to notify the manufacturer of any changes in the product or service so that manufacturers may determine whether the change may affect the quality of a finished device. Each manufacturer shall review and approve purchasing data for adequacy of the specified requirements prior to release. The approval, including the approval date and signature of the individual(s) approving the data, shall be documented.

<A NAME="rSubpart F">Subpart F--Identification and Traceability</A>

820.60 Identification.

Each manufacturer shall establish and maintain procedures for identifying product during all stages of receipt, production, distribution, and installation to prevent mixups.

820.65 Traceability.

Each manufacturer shall establish and maintain procedures for identifying each unit, batch, or lot of finished devices and components with a control number where necessary to ensure the protection of the public health. The procedures shall facilitate corrective action. Such identification shall be recorded in the device history record.

<A NAME="rSubpart G">Subpart G--Production and Process Controls</A>

820.70 Production and process controls.

(a) General. Each manufacturer shall design, conduct, control, and monitor production processes to ensure that a device conforms to its specifications. Where deviations from device specifications could occur as a result of the manufacturing process, the manufacturer shall establish and maintain process control procedures that describe any process controls necessary to ensure conformance to specifications. Process controls shall include:

(1) Documented instructions, standard operating procedures (SOP's), and methods that define and control the manner of production;

(2) Monitoring and control of process parameters and component and device characteristics during production;

(3) Compliance with applied reference standards or codes and process control procedures;

(4) The approval of processes and process equipment; and,

(5) Criteria for workmanship which shall be expressed in documented standards or by means of representative samples.

(b) Production and process changes. Each manufacturer shall establish and maintain

procedures for changes to a specification, method, process, or procedure. Such changes shall be validated before approval and implementation, unless inspection and test fully verifies the results of the changes. The results of the validation, or verification, shall be documented. Approved changes shall be communicated to the appropriate personnel in a timely manner.

(c) Environmental control. Each manufacturer shall establish and maintain requirements for the environment to which product is exposed. Where environmental conditions could have an adverse effect on a device's fitness for use, these environmental conditions shall be controlled, and procedures for such controls shall be established and maintained. Any environmental control system shall be periodically inspected to verify that the system is adequate and functioning properly. Results of such inspections shall be documented and reviewed.

(d) Personnel. Each manufacturer shall establish and maintain requirements for health, cleanliness, personnel practices, and clothing of personnel if contact between such personnel and product or environment could adversely affect the quality of the product. The manufacturer shall ensure that all personnel who are required to work temporarily under special environmental conditions are appropriately trained or supervised by a trained individual.

(e) Contamination control. Each manufacturer shall establish and maintain procedures to prevent contamination of equipment or product by substances that could adversely affect device safety or effectiveness.

(f) Buildings. Buildings shall be of suitable design and contain sufficient space to perform necessary operations, prevent mixups, and assure orderly handling.

(g) Equipment. Each manufacturer shall ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use.

(1) Maintenance schedule. Each manufacturer shall establish and maintain schedules for the maintenance, adjustment, and cleaning of equipment to ensure that manufacturing specifications are met. Records shall be maintained documenting the date when scheduled maintenance activities were performed and the individual(s) performing the maintenance activity.

(2) Inspection. Each manufacturer shall conduct periodic inspections in accordance with established procedures to ensure adherence to applicable equipment maintenance schedules. The inspections, including the date and individual conducting the inspections, shall be documented.

(3) Adjustment. Each manufacturer shall ensure that any inherent limitations or allowable tolerances are visibly posted on or near equipment requiring periodic adjustments or are readily available to personnel performing these adjustments.

(h) Manufacturing material. Each manufacturer shall establish and maintain procedures for the use and removal of manufacturing material to ensure that such material is removed from the device or limited to a specified amount that does not adversely affect the device's quality. The removal of such manufacturing material shall be documented.

(i) Automated processes. When computers are used as part of production, the quality system, or automated data processing systems, the manufacturer shall validate computer software for its intended use according to an established protocol. The results shall be documented. All software changes shall be validated before approval and issuance. The results shall be documented.

820.75 Process validation.

(a) Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated according to established procedures. Records shall be made of the validation activities and results, including the date and individual(s) performing the validation.

(b) Each manufacturer shall establish and maintain procedures for continuous monitoring and control of process parameters to ensure that the specified requirements are met.

(c) Each manufacturer shall ensure that validated processes are performed by qualified individual(s).

(d) Records shall be maintained for the validated processes to include monitoring and control methods and data, signature of the individual(s) performing the process, the date performed, and where appropriate, the major equipment used.

<A NAME="rSubpart H">Subpart H--Acceptance Activities</A>

820.80 Receiving, in-process, and finished device acceptance.

(a) General. Each manufacturer shall establish and maintain the acceptance activities necessary to ensure that specified requirements are met. Acceptance activities include inspections, tests, and other verification activities.

(b) Receiving acceptance activities. Each manufacturer shall establish and maintain procedures for acceptance of incoming product. Incoming product shall be inspected or otherwise verified as conforming to specified requirements. Acceptance and rejection shall be documented.

(c) In-process acceptance activities. Each manufacturer shall establish and maintain acceptance procedures to ensure that specified requirements for in-process product are met. Such procedures shall ensure that in-process product is held until the required inspection and tests or other verification activities have been completed, or necessary approvals are received, and are documented.

(d) Final acceptance activities. Each manufacturer shall establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets specified requirements. Finished devices shall be held in quarantine or otherwise adequately controlled until released. Finished devices shall not be released for distribution until the required activities specified in the DMR are completed, the associated data and documentation is reviewed, and release is authorized by the signature of a designated individual(s). Such authorization shall be dated.

(e) Acceptance records. Each manufacturer shall maintain records of the results of acceptance activities required by this part. These records shall include the acceptance criteria, acceptance activities performed, dates performed, results, the signature of the individual(s) conducting the acceptance activities and, where appropriate, equipment used. These records shall be part of the device history record.

820.84 Inspection, measuring, and test equipment.

Each manufacturer shall ensure that all measurement and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results. Each manufacturer shall establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained. Records documenting these activities shall be maintained.

(a) Calibration. Calibration procedures shall include specific directions and limits for accuracy and precision. There shall be provisions for remedial action when accuracy and precision limits are not met.

(b) Calibration standards. Calibration standards used for measurement equipment shall be traceable to national or international standards. If national or international standards are not practical or available, the manufacturer shall use an independent reproducible standard. If no applicable standard exists, the manufacturer shall establish and maintain an in-house standard.

(c) Calibration records. Each manufacturer shall ensure that records of calibration dates, the individual performing each calibration, and the next calibration date are maintained. These records shall be displayed on or near each piece of equipment or shall be readily available to the personnel using such equipment and the individuals responsible for calibrating the equipment.

(d) Maintenance. Maintenance procedures shall include provisions for handling, preservation, and storage of inspection, measuring, test equipment, and test software so that their accuracy and fitness-for-use are maintained.

820.86 Acceptance status.

Each manufacturer shall identify by suitable means the acceptance status of product, to indicate the conformance or nonconformance of these items with respect to acceptance criteria. The identification of acceptance status shall be maintained throughout component acceptance, manufacturing, packaging, labeling, installation, and servicing of the product to ensure that only products which have passed the required acceptance activities are distributed, used, or installed.

<A NAME="rSubpart I">Subpart I--Nonconforming Product </A>

820.90 Nonconforming product.

(a) Control of nonconforming product. Each manufacturer shall establish and

maintain procedures to ensure that product that does not conform to specified requirements is not used or distributed. The procedures shall provide for the identification, documentation, evaluation, segregation, and disposition of nonconforming product. The procedures shall provide for the investigation of nonconformances and notification of the persons or organizations responsible for the nonconformance.

(b) Nonconformity review and disposition. (1) Each manufacturer shall establish and maintain procedures that define the responsibility for review and the authority for the disposition of nonconforming product. The procedures shall set forth the review and disposition process. Nonconforming disposition shall be documented to include the justification for any concession and the signature of the individual(s) authorizing the concession.

(2) Each manufacturer shall establish and maintain procedures for the reprocessing, to include retesting and reevaluation of the nonconforming product after reprocessing, to ensure that it meets its original, or subsequently modified and approved, specifications. Reprocessed product shall be clearly identified during reprocessing, and shall be subjected to reevaluation. The reprocessing and reevaluation results shall be recorded in the device history record. When there is reprocessing of a product, a determination of the effect of the reprocessing upon the product shall be made and documented.

<A NAME="rSubpart J">Subpart J--Corrective and Preventive Action</A>

820.100 Corrective and preventive action.

(a) Each manufacturer shall establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements for:

(1) Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed to detect recurring quality problems;

(2) Investigating the cause of nonconformities relating to product, process, and quality system;

(3) Identifying action needed to correct the cause and prevent recurrence of nonconforming product and other quality problems;

(4) Verifying or validating the adequacy of the corrective and preventive action to ensure that the corrective and preventive action does not adversely affect the finished device and that such action is effective;

(5) Implementing and recording changes in methods and procedures needed as a result of the identification of quality problems, and corrective and preventive action;

(6) Ensuring that information related to nonconforming product or quality problems is disseminated to those directly responsible for assuring the quality of such product or the absence of such problems; and

(7) Confirming that relevant information on actions taken is submitted for management review.

(b) All activities required under this section, and their results, shall be documented.

<A NAME="rSubpart K">Subpart K--Handling, Storage, Distribution, and Installation

820.120 Handling.</A>

Each manufacturer shall establish and maintain procedures to ensure that mixups, damage, deterioration, or other adverse effects to product do not occur during handling.

820.122 Storage.

(a) Each manufacturer shall establish and maintain procedures for the control of storage areas and stock rooms for product to prevent mixups, damage, deterioration, or other adverse effects pending use or distribution and to ensure that all obsolete, rejected, or deteriorated product is not used or distributed.

(b) Each manufacturer shall establish and maintain procedures that describe the methods for authorizing receipt from and dispatch to such designated areas. When the quality of product deteriorates over time, it shall be stored in a manner to facilitate proper stock rotation, and its condition shall be assessed at appropriate intervals.

820.124 Distribution.

(a) Each manufacturer shall establish and maintain procedures for control and distribution of finished devices to ensure that only those devices approved for release are distributed. Where a device's fitness-for-use or quality deteriorates over time, the procedures shall ensure that expired devices or devices deteriorated beyond acceptable fitness for use are not distributed.

(b) Each manufacturer shall maintain distribution records which include or refer to the location of:

(1) The name and address of the initial consignee;

(2) The identification and quantity of devices shipped, the date shipped; and

(3) Any control number(s) used for traceability, if required by 820.65.

820.126 Installation.

Each manufacturer of a device requiring installation shall establish and maintain adequate instructions and procedures for proper device installation. Instructions and procedures shall include directions for ensuring proper performance of the installation and that the device will perform as intended after installation. The manufacturer shall ensure that the installation instructions and inspection procedures are distributed with the device or otherwise available to the person(s) installing the device. The person installing the device shall ensure that the installation was performed in accordance with the manufacturer's instructions and procedures and shall record the inspection results to demonstrate proper installation. The results of the installation inspection shall made available to FDA upon request.

<A NAME="rSubpart L">Subpart L--Packaging and Labeling Control</A>

820.160 Device packaging.

Each manufacturer shall ensure that device packaging and shipping containers are designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution.

820.162 Device labeling.

Each manufacturer shall establish and maintain procedures to maintain labeling integrity and to prevent labeling mixups.

(a) Label integrity. Each manufacturer shall ensure that labels are printed and, where applicable, applied so as to remain legible and affixed to the device during the customary conditions of processing, storage, handling, distribution, and use.

(b) Labeling inspection. Labeling shall not be released for storage or use until a designated individual(s) has examined the labeling for accuracy including, where applicable, the correct expiration date, control number, storage instructions, handling instructions, and additional processing instructions. The release, including the date and signature of the individual(s) performing the examination, shall be documented in the device history record.

(c) Labeling storage. Each manufacturer shall store and maintain labeling in a manner that provides proper identification and is designed to prevent mixups.

(d) Labeling operations. Each manufacturer shall control labeling and packaging operations to prevent labeling mixups.

(e) Control number. Where a control number is required by 820.65, that control number shall be on the device itself or its label.

<A NAME="rSubpart M">Subpart M--Records</A>

820.180 General requirements.

All records required by this part shall be maintained at the manufacturing establishment or other location that is reasonably accessible to responsible officials of the manufacturer and to employees of the Food and Drug Administration designated to perform inspections. Such records, including those not stored at the inspected establishment, shall be made readily available for review and copying by FDA employee(s). Such records shall be legible and shall be stored to minimize deterioration and to prevent loss. Those records stored in automated data processing systems shall be backed up.

(a) Confidentiality. Records deemed confidential by the manufacturer may be marked to aid the Food and Drug Administration in determining whether information may be disclosed under the public information regulation in part 20 of this chapter.

(b) Record retention period. All records required by this part shall be retained for a period of time equivalent to the design and expected life of the device, but in no case less

than 2 years from the date of release for commercial distribution by the manufacturer.

(c) Exceptions. This section does not apply to the reports required by 820.20(c) and 820.22, and supplier audit reports used to meet the requirements of 820.50(a), but does apply to procedures established under these subsections. Upon request of a designated employee of the Food and Drug Administration, an employee in management with executive responsibility shall certify in writing that the management reviews and quality audits required under this part, and supplier audits where applicable, have been performed and documented, the dates on which they were performed, and that any required corrective action has been taken.

820.181 Device master record.

Each manufacturer shall maintain device master records (DMRs). Each manufacturer shall ensure that each DMR is prepared, dated, and approved with the signature of the qualified individual(s) designated by the manufacturer. The DMR for each type of device shall include, or refer to the location of, the following information:

(a) Device specifications including appropriate drawings, composition, formulation, component specifications, software specifications, and software source code for customized software;

(b) Production process specifications including the appropriate equipment specifications, production methods, production procedures, and production environment specifications;

(c) Quality assurance procedures and specifications including quality assurance checks used, and the quality assurance apparatus used;

(d) Packaging and labeling specifications, including methods and processes used; and

(e) Installation, maintenance, and servicing procedures and methods.

820.184 Device history record.

Each manufacturer shall maintain device history records (DHRs). Each manufacturer shall establish and maintain procedures to ensure that DHRs for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the DMR and the requirements of this part. The DHR shall include, or refer to the location of, the following information:

(a) The dates of manufacture;

(b) The quantity manufactured;

(c) The quantity released for distribution;

(d) The specific label and labeling used for each production unit; and

(e) Any device identification(s) and control number(s) used.

820.186 Quality system records.

Each manufacturer shall maintain quality system records to demonstrate conformance to specified requirements and effective operation of the quality system as defined in 820.5, to include or refer to the location of:

(a) Documentation of activities that establish the objectives and requirements for quality, and the application of quality system elements;

(b) Documentation of the responsibilities, authorities, and interrelationships of personnel who manage, perform, verify, or review work affecting quality;

(c) The quality system procedures and instructions; and

(d) An outline of the structure of the documentation used in the quality system, where appropriate.

820.198 Complaint files.

(a) Each manufacturer shall maintain complaint files. Each manufacturer shall establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit. Such procedures shall ensure that:

(1) All complaints are processed in a uniform and timely manner;

(2) Oral complaints are documented upon receipt; and

(3) Complaints are evaluated to determine whether the complaint represents an event which is required to be reported to the Food and Drug Administration under part 803 of this chapter, Medical Device Reporting.

(b) Each manufacturer shall review and evaluate all complaints to determine whether an

investigation is necessary. When no investigation is made, the unit shall maintain a record that includes the reason no investigation was made and the name of the individual responsible for the decision not to investigate.

(c) Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated.

(d) Any complaint pertaining to death, injury, or any hazard to safety shall be immediately reviewed, evaluated, and investigated by a designated individual(s) and shall be maintained in a separate portion of the complaint files or clearly and visibly identified as pertaining to a death, injury, or hazard to safety. Such investigations shall also include a determination of whether there was an actual device failure to perform pursuant to specifications, whether the device was being used to treat or diagnose a patient, and the relationship, if any, of the device to the reported incident or adverse event.

(e) When an investigation is made under this subpart, a written record of each investigation shall be maintained by the formally designated unit identified in paragraph (a) of this section. The record of investigation shall include:

(1) The name of the device;
(2) The date the complaint was received;
(3) Any device identification(s) and control number(s) used;
(4) The name, address, and phone number of the complainant;
(5) The nature and details of the complaint;
(6) The dates and results of the investigation;
(7) Any corrective action taken; and
(8) Any reply to the complainant.

(f) When the manufacturer's formally designated complaint unit is located at a site separate from the actual manufacturing establishment, the complaint and the record of investigation shall be concurrently maintained at the actual manufacturing establishment in a file designated for device complaints.

(g) If a manufacturer's formally designated complaint unit is located outside of the United States, records required under this section shall be concurrently maintained in the United States at either:

(1) A location in the United States where the manufacturer's records are regularly kept; or

(2) The location of the agent designated by the manufacturer under 803.26(g)(2) of this chapter [as proposed in the Federal Register of November 26, 1991 (56 FR 60024)].

<A NAME="rSubpart N">Subpart N--Servicing</A>

820.200 Servicing.

Each original manufacturer (including a refurbisher) shall establish and maintain instructions and procedures to ensure that finished devices that are serviced meet safety and performance specifications for the original intended use of the device(s). The instructions and procedures shall include directions for ensuring that the device(s) will perform as intended after servicing. Such manufacturer shall ensure that the device's safety and performance specifications, to include the device's end-of-life date or period, accompany the device at the time of the initial sale or are otherwise made available to the person(s) servicing the device. Procedures for servicing shall include provisions for determining if service requests represent an event which must be reported to the Food and Drug Administration under the requirements of part 803 of this chapter.

(a) Service reports. Each person that services a device shall establish and maintain procedures to ensure that service reports are maintained and identify the device serviced, including any device identification(s) and control number(s) used, the date of service, the service performed, and individual(s) servicing the device. Service reports shall be recorded and made available to FDA upon request. Such reports shall demonstrate that the finished device serviced meets the manufacturer's safety and performance specifications. A copy of all service reports shall be forwarded to the original manufacturer.

(b) Service report evaluation. Each original manufacturer shall analyze service reports with appropriate statistical methodology in accordance with 820.100; however, when a service report involves a death, injury, or hazard to safety, the report shall automatically be considered a complaint and shall be investigated in accordance with the requirements of 820.198.

<A NAME="rSubpart O">Subpart O--Statistical Techniques</A>

820.250 Statistical techniques.

(a) Where appropriate, each manufacturer shall establish and maintain procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics.

(b) Sampling plans, when used, shall be written and based on a valid statistical rationale. Each manufacturer shall establish and maintain procedures to ensure that sampling methods are adequate for their intended use and are regularly reviewed.

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APPLICATION OF THE MEDICAL DEVICE GMPS TO COMPUTERIZED DEVICES AND MANUFACTURING PROCESSES

MEDICAL DEVICE GMP GUIDANCE FOR FDA INVESTIGATORS

Prepared by
Office of Compliance and Surveillance
Division of Compliance Programs

November 1990

FIRST DRAFT

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
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Application of Medical Device GMPs to Computerized Devices and Manufacturing Processes

1.0 PURPOSE

This document outlines GMP requirements as applied to the manufacture of computerized devices and the control of computerized manufacturing and quality assurance systems. It is intended to provide guidance to FDA investigators and to supplement FDA document 84-4191, Medical Device GMP Guidance for FDA Investigators.[1] This document is also designed to supplement FDA issued compliance policy statements and references on Software Development Activities Policy Guides[2] and FDA's Technical Reference on Software Development Activities.[3]

2.0 SCOPE

This document applies to manufacturers who utilize automated systems for manufacturing, quality assurance, and/or recordkeeping. It also applies to manufacturers of medical devices that are driven or controlled by software.

3.0 INTRODUCTION

The GMP contains requirements which assure that specifications are established for the device, components, labeling, and packaging and that these specifications are met. The GMP is written in general terms in order that it may apply to a broad diversity of medical devices and manufacturing processes found in the medical device industry. Because of this, FDA investigators sometimes have difficulty in applying the GMP to certain aspects of the industry. Automation is one area where investigators have expressed difficulty in applying the GMP, whether it is automation of individual devices or automation of a manufacturing system.

This document is intended to assist investigators in properly interpreting and applying the GMP to this industry. However, investigators should understand that while the procedures and controls described in this document are acceptable to FDA, they may not be the only procedures and controls acceptable to FDA. Manufacturers are free to use other approaches as long as they can provide assurance that they are adequate in meeting the applicable GMP requirements.

4.0 APPLICATION OF THE GMP

4.1 General

In order to assure that only safe and effective devices are distributed, devices must be designed and manufactured under adequate quality assurance controls. The following is a section-by-section discussion of the GMP as it applies to computers and describes the types of controls that would

Per Part 820.20(a)(2) each manufacturer is responsible for assuring the acceptability of components and labeling, as well as the finished device, regardless of whether they are manufactured in-house or provided under contract by another company (vendor supplied). Therefore, a manufacturer's quality assurance program includes procedures for assuring approval or rejection of contract-supplied software.

To assure that only acceptable software is received, manufacturers who purchase software from vendors establish a program for assuring that the vendor has demonstrated a capability to produce quality software. The program provides assurance that the requirements for the software are clearly defined, communicated and completely understood by the vendor. This may require written procedures for the preparation of requirements and purchase orders, vendor conferences prior to contract release and other appropriate methods. In order to assure understanding, manufacturers establish a close working relationship and feedback system with the vendor. In this way a program of continual quality improvements can be maintained and quality disputes avoided or settled quickly.

Acceptance procedures for contract-supplied software may vary. For example, they may include third-party certification. The finished device manufacturer, however, has the primary responsibility for assuring the software is adequate for its intended use. When third-party certification is used, the certification package includes adequate documented evidence that the software complies with specified requirements. Examples of such evidence include documentation of the review, including procedures used to evaluate the software, the results of the evaluation and evidence of the decision-making process used by the manufacturer to conclude that the software will fulfill its requirements. When the contract-supplied software includes more functions than are utilized, those portions of the program which will be used are evaluated for their application. Also, the software is evaluated to assure the unused portions do not interfere with proper performance. Specific requirements which apply to these activities are covered under 820.80(a), 820.160, and 820.161 and are discussed later in this document.

Part 820.20(a)(3) requires manufacturers to identify quality assurance problems and to verify the implementation of solutions to those problems. Thus, quality data collected by a firm through its various documented process and control systems, such as work operations, processes, quality records, service reports and customer complaints, are evaluated by appropriate methods (e.g.,

Other forms of preprogrammed media such as disks (hard and floppy) and magnetic tapes are also handled only in environmentally controlled areas. In areas where these are used, the ability to retrieve data may also be adversely affected by exposure to dust and dirt; therefore, dust and dirt is controlled in addition to ESD.

Components and other media are protected from sources of magnetic interference which can result in the potential accidental erasure of the software by a magnetic field from a permanent magnet or electromagnet. If the product is electromagnetic interference (EMI) sensitive, then efforts to control and/or test for EMI are documented.

4.5 Equipment (820.60)

Section 820.60 of the GMP mandates periodic maintenance of equipment used in the manufacturing process, when applicable. When applied to the software used in production, working master copies of software are periodically challenged and compared against the archived master as a means of assuring that the working copy of the released version is a true copy of the master. Unauthorized changes may compromise the accuracy and reliability of the process.

Comparison of two or more computer programs may be accomplished by a number of different procedures. One common method uses a software utility program which compares two programs and prints differences found between them. A comparison of disk directories between the master and working copies as well as the use of some comparative programs can assist in identifying the differences. The differences may be as simple as one copy containing additional utility programs while the others do not. Another procedure involves comparing the checksums of the preprogrammed chips. The checksum is the value which results from the addition of the values stored in each address on the chip. The values from each chip of the working copy are then compared with the checksums of the archived master. Any difference between the two reflects a discrepancy in the programs and indicates a change in either of the two copies, but it does not identify the location of the difference(s). This is accomplished separately.

Only the current version of software that has been approved and released for use by the device manufacturer is available in the manufacturing/quality control area. When software revisions have been made and released for use, obsolete versions of the program are removed from use. Appropriate corresponding documentation (e.g., written manufacturing procedures and/or design specifications) is also updated and distributed in a timely manner.

After it is determined that the software is acceptable for use, consideration is given to the need for periodic retests. Retests are usually necessary when the software (operating system or application program) is revised or a software failure is encountered.

When preprogrammed storage media such as chips, disks, etc., are received as components, acceptance procedures assure that software contained in these components is the current version and that it has been adequately duplicated. Acceptance evaluation can be accomplished in a number of ways. One method is a bit-by-bit comparison of the software program in the incoming component against a known correct master copy of the program. Another method consists of determining the checksum of the software in the incoming component and comparing it against the known checksum for the current version of the program. (This test method has been previously discussed in the "Equipment" section of this document; however, the method is also applicable to acceptance of components.) These tests only assure accuracy of the reproduction efforts; they do not reflect the quality of the software program, which can only be determined through the verification and validation test efforts previously discussed.

Incoming acceptance procedures for unprogrammed (blank) ICs vary. They may consist of electrical tests or only a visual examination, depending upon whether history has demonstrated that the supplier can consistently provide a quality product.

Some medical device manufacturers may purchase OEM (Original Equipment Manufacture) products such as CRTs, computers, etc., and combine these products into a medical device system. These may be considered components rather than finished devices. In such cases, it is the medical device manufacturer's responsibility to assure the OEM products are acceptable for use. This may include testing the products individually and as part of the finished system to assure they conform to specifications.

4.7.2 Storage and Handling of Components (820.80(b))

As with all finished device components, software must be adequately identified to prevent mix-up and adequately stored to prevent damage.

Software contained on media such as disks, etc., is identified by providing name or title and version or revision level of the software. This serves to prevent use of obsolete versions of the program.

When a manufacturing process is controlled by computer, functional evaluation of the control system may include, but is not limited to, the following activities:

- o equipment (peripherals, etc.) and sensor checks using known inputs, which may consist of processing test or simulated data;
- o alarm checks at, within, and beyond their operational limits; and,
- o evaluation of operator override mechanisms for how they are used by operators and how they are documented.

In case of system failure, evaluations would include:

- o how data is updated when in manual operation;
- o what happens to data "in process" when the system shuts down;
- o what procedures are in place to handle system shutdown; and,
- o how product or information handled by the computerized process is affected.

Process validation is conducted to evaluate the effectiveness and repeatability of the process and its impact on the device during both expected operation and worst case situations. When software is involved, this activity may in many cases have to be accomplished in two steps: first, the software is integrated into the system and the system is evaluated independently of the system it is to control; second, the software is integrated into the system and the system is evaluated.

Section 820.100(a)(2) requires that changes to specifications of a device, which includes software specifications, must be subject to controls as stringent as those applied to the original software program. Usually, this means validation that includes an evaluation of how the change impacts on the rest of the software. For example, if the addition of a subroutine or function is determined to have little effect on the device or process, only a limited number of modules may require retesting and revalidation. On the other hand, changes such as updating the operating system software could have an impact on the entire application software, thereby requiring more intensive evaluation. In any event, all changes are evaluated to assure that they are appropriate (that they achieve their intended purpose) and that they do not adversely affect the unchanged software.

Revisions to software follow established change control procedures to assure that the history of the changes are

If the software error is in the device, similar investigative activities are conducted. In either situation, the investigation extends to determining effects on other products, and results in a written record of the investigation and any follow-up action and corrective action taken.

4.12 Records, General Requirements (820.180)

Recordkeeping requirements that apply to nonautomated devices also apply to software controlled devices. Records must be available for review and copying by FDA employees, including those records which have been computerized and placed on computer storage media such as magnetic tape, disks, etc.

All records maintained in accordance with 21 CFR 820 are required to be retained for a period of time equivalent to the design and expected life of the device, but in no case less than two years from the date of release of the device for commercial distribution.

4.13 Device Master Record (820.181)

The device master record (DMR) consists of diagrams, descriptions, schematics, etc., that constitute the specifications for the medical device product, the manufacturing process, and QA program. In addition to items detailing specifications for the device hardware, the device master record for a software driven product also includes detailed specifications for the device software. Detailed specifications are also required when the device consists of only software.

All records and documents contained in the device master record are controlled documents, including documentation related to software. Any revision or change of the software program or its supporting documentation are made in accordance with formal change control procedures and authorized by signature of the designated individual(s). Magnetically coded badges and other electronic identifiers may be used in lieu of signatures if adequate controls are in place to prevent their misuse.

4.13.1 Specifications (820.181(a))

The device master record must include specifications for the device. When software is part of the device, specifications include or refer to:

- the final, complete, approved software design requirements, which describe in narrative and/or pictorial form, such as a flow chart, what the software is intended to do (e.g., to control or monitor something) and how it will accomplish these tasks. Also included is a description of how the software will interact with the hardware to

that manufacturing and test procedures have been followed and that the results meet acceptance criteria. When software is part of the device, this documentation includes a record of the version of the software which was assembled into the device, results from evaluating the device software (e.g., performance), in addition to all documentation needed to show that the software was adequately reproduced during manufacturing.

Adequate production records are in place to properly document all significant activities. For example, software that is part of a device may be copied into components, such as PROMs (Programmable Read Only Memory Chips), which are then assembled into the device. Production records for this activity document the results of the duplication process. For example, when checksums are used to identify the revision of the software which is duplicated into components, the production record documents the checksum and the number of components which were copied as well as the date the activity was performed. All production records are included in, or referred to in, the device history record.

4.15 Critical Devices, Automated Data Processing (820.195)

Section 820.195 applies only to manufacturing or quality assurance activities associated with critical devices. Automated data processing is the means used to gather and analyze information on some characteristic of the device manufacturing process or QA program without direct use of an operator to control the activity or verify the results. Automated data processing systems provide an effective method for performing routine, repetitive tasks. Although generally more reliable than manual equivalents, such systems demand adequate controls for equipment setup and programming. The GMP regulation requires a manufacturer to implement controls that will assure the correctness and appropriateness of these programs, program changes, equipment and data input and output.

4.16 Complaint Files (820.198)

Firms must prepare and implement adequate complaint handling systems including the review, investigation, and evaluation of both hardware and software failures of distributed devices. A notation in the complaint file that a system has failed as a result of a software error is supported with data or evidence to justify that conclusion. When a software failure is encountered, an investigation is conducted to determine the cause of the error and its impact on the capabilities of the device and similar devices.

Many manufacturers use computers for recording and tracking complaint information contained in paper documents, such as letters from complainants or laboratory reports. The complete information may be copied into the computer system in lieu of

PROM Programmer	Electronic equipment which is used to transfer a software program into a PROM.
Third-Party Certification	The procedure and action, by a duly authorized independent body, of confirming that a system, software subsystem, or computer program is capable of satisfying its specified requirements in an operational environment. Certification usually takes place in the field under actual or simulated operational conditions, and is used to evaluate the software itself and the specifications to which the software was designed. Certification activities take place under a written, approved (by the manufacturer) protocol.
Validation	Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.
Validation Testing	Testing that commences after the completion of the development testing and includes module and subsystem level testing. These tests can be considered to be "rehearsals;" they are basically gross tests of the coding against specifications.
Verification	The process of reviewing, inspecting, testing, checking, auditing, or otherwise establishing and documenting whether or not items, processes, services, or documents conform to specified requirements.
Verification Testing	An acceptance test of software. These tests are rigorous and detailed and will result in the software quality certification that the coding is in complete agreement with the specifications, design, and test documentation.
Worst Case	A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

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FDA 87-4179: CDRH, Device Good Manufacturing Practices Manual, 4th Edition, Division of Small Manufacturers Assistance, OTA (November 1987).

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FDA 90-4236: CDRH, Preproduction Quality Assurance Planning; Recommendations for Medical Device Manufacturers, Office of Compliance and Surveillance, Division of Compliance Programs (September 1989).

* U.S. GOVERNMENT PRINTING OFFICE: 1996-721-547/83139