Drugs

Pharmaceutical CGMPs for the 21st Century — A Risk-Based Approach: Second Progress Report and Implementation Plan

Introduction

On February 20, 2003, the Food and Drug Administration (FDA) released its first progress report on a major initiative concerning the regulation of drug product quality. The 2-year initiative, Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach (the Pharmaceutical CGMP initiative), which was launched on August 21, 2002, applies to human drug and biological drug products and veterinary drugs and has several objectives:

- To encourage the early adoption of new technological advances by the pharmaceutical industry
- To facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance
- To ensure that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science
- To enhance the consistency and coordination of FDA's drug quality regulatory programs, in part, by integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities

During an April 2003 inaugural scientific workshop that was held with stakeholders in Washington, DC, FDA received many valuable comments and ideas (workshop summary). Input from this workshop and other meetings, such as FDA Science Board and Advisory Committee for Pharmaceutical Science, have supported the progression and evolution of the initiative during the past year, enabling the Agency to make substantial progress in its initiative. The Pharmaceutical CGMP initiative was made an important component of the science-based risk management goal in the Agency’s August 20, 2003, S-Part Strategic Action Plan to Protect and Advance America’s Health. The progress of the CGMP initiative to date and plans for the future are the focus of this report.

Brief Progress Report on Our Achievements to Date

As a result of the input received at various meetings and of progress made during the past year on the Pharmaceutical CGMP initiative, new working groups have been formed and some of the original working groups have been realigned. These multidisciplinary groups, comprising experts from various areas of scientific and regulatory practice, are shaping and implementing the initiative under the oversight of the FDA CGMP Steering Committee. (Pharmaceutical Working Groups)

The working groups have completed the following 5 guidance documents, which the Agency is announcing with this progress report:

- Part 11, Electronic Records, Electronic Signatures - Scope and Application (final guidance)
- Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMPs (draft guidance)
- Sterile Drug Products Produced by Aseptic Processing (Part 11, Electronic Records, Electronic Signatures - Scope and Application) (draft guidance)
- Comparability Protocols - Protein Drug Products and Biological Products, Chemistry, Manufacturing, and Controls Information (draft guidance)
- PAT - A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance (draft guidance)

In addition, the Agency has recently entered into the following collaborations with industry, academia, and another governmental organization. Details of these collaborations are discussed further in this paper:

- The Office of Regulatory Affairs (ORA) and the Center for Drug Evaluation and Research (CDER) recently signed a memorandum of understanding establishing a Pharmaceutical Inspectorate within ORA. Details of this highly trained staff are discussed later in the report.
- The Preapproval Inspection Compliance Program has been revised to give the field more flexibility and provide for enforcement under certain circumstances. The final guidance addresses the comments received during the comment period, including those concerning enforcement discretion, time stamps, and legacy systems. The guidance explains the goals of this initiative and removes barriers to scientific and technological advances and encourages the use of risk-based approaches. The Agency intends to begin rulemaking to revise Part 11, to provide further clarification and adjustments consistent with the principles and enforcement policies described in this guidance document.

21 CFR Part 11 - Electronic Records Requirements

The final guidance for industry Part 11, Electronic Records, Electronic Signatures - Scope and Application clarifies the scope and application of the Part 11 regulation and provides for enforcement discretion in certain areas. The final guidance addresses the comments received during the comment period, including those concerning enforcement discretion, time stamps, and legacy systems. The guidance explains the goals of this initiative and removes barriers to scientific and technological advances and encourages the use of risk-based approaches. The Agency intends to begin rulemaking to revise Part 11, to provide further clarification and adjustments consistent with the principles and enforcement policies described in this guidance document.

Implementation of a Technical Dispute Resolution Process for CGMP Disputes

The draft guidance Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP is intended to provide recommendations to manufacturers of veterinary and human drugs, including human biological drug products, on how to resolve disputes about scientific and technical issues relating to current good manufacturing practice (CGMP) regulations. Disputes related to scientific and technical issues may arise during FDA inspections of pharmaceutical manufacturers to determine compliance with CGMP requirements or during the Agency's assessment of corrective actions undertaken as a result of such inspections. Because these disputes may involve complex scientific and technical issues, it is important to have a process in place that encourages open, prompt discussions and leads to dispute resolution. Once finalized, the Dispute Resolution guidance will describe procedures for raising such disputes to the Office of Regulatory Affairs (ORA) and Agency centers and for requesting review by the Dispute Resolution Panel for Scientific and Technical Issues Related to Pharmaceutical CGMPs.

By January 1, 2004, the Agency intends to initiate a 12-month domestic pilot program consistent with the guidance document. The publication of the final guidance is targeted for January 2005 and will reflect the completion and evaluation of the pilot as well as the review of any comments received.

Science-Based Policies and Procedures to Facilitate Innovation Within the Existing Regulatory Framework

Aseptic Processing Guidance Undergoing Revision

Once finalized, the draft guidance Sterile Drug Products Produced by Aseptic Processing -- Current Good Manufacturing Practice will replace the 1987 Guidance on Sterile Drug Products Produced by Aseptic Processing and provide recommendations on how to build quality into products using science-based facility, equipment, and systems design. There are two risk-related themes in the draft guidance:

- Ensure that operational inputs are predictable through adequate quality control and quality assurance
- Ensure reliable and robust product protection through adequate design and control

These objectives are consistent with modern manufacturing trends. In particular, the draft guidance underscores the advantages that automation and isolation concepts offer in protecting the exposed sterile drug product during its aseptic manufacturing.

Sterile drug products are a high priority in our current risk-based inspectional program. These drug products are generally of high therapeutic significance, and our proactive efforts to enhance CGMP understanding in this area are intended to promote CGMP compliance and ensure a steady supply of these medically necessary products to the U.S. consumer.

As the Agency continues to monitor the incidence of manufacturing problems with this class of pharmaceuticals, which are often a major cause of drug shortages, it is clear that a science-based approach is the most effective approach. The guidance also is consistent with Agency efforts to harmonize with international regulatory standards and develop more science-based guidance documents.

Preapproval Inspection Priorities Revised

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FDA has revised and reduced the number of inspection categories that would automatically prompt an inspection when a drug application or supplement is reviewed by the Agency. To implement the change, the Agency has revised this section of the Preapproval Inspection Compliance Program[11] [PDF] and notified Corporate Safety and Regulatory managers and Agency personnel conducting preapproval inspections (PAIs) of changes.

By reducing the number of mandatory inspection categories, ORA field offices have greater flexibility in determining if a preapproval inspection is warranted. This change is effective immediately and has been incorporated into the Compliance Program for Preapproval Inspections/Investigations, CP 7346.832. These changes will help reduce the number of preapproval inspections being carried out, providing additional resources for more high-risk preapproval and postapproval CGMP inspection coverage. Additional changes to provide more flexibility in assigning preapproval inspections consistent with our risk-based approach are under consideration.

**Comparability Protocols Offered as an Option**

The draft guidance **Comparability Protocols Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information**[12], describes recommendations for preparing and using pre-defined change evaluation plans, generally referred to as comparability protocols, to implement preapproval manufacturing changes. Once finalized, the guidance will apply to protein-based human and veterinary drug products and biological products. Under appropriate circumstances, use of an approved comparability protocol can allow manufacturers to implement some changes without submission of a prior approval supplement. Having inspection data and the protocol will enable the Agency to ensure that the regulatory requirements appropriately target the risk that a manufacturing change will adversely affect product quality. We also plan to finalize in early 2004 the February 2003 draft guidance pertaining to nonprotein human and veterinary drugs.

In addition, we are planning an evaluation of existing data on prior approval changes with the goal of identifying opportunities for reducing application submission and filing requirements. Throughout 2004, ongoing postapproval activities will be evaluated to identify opportunities for improving coordination between review and inspection activities to identify and implement opportunities for managing manufacturing changes without the need for prior FDA review or approval.

**PAT - a New Framework to Encourage Manufacturing Innovation**

The draft guidance **PAT - A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance**[13] is intended to describe a regulatory framework that should encourage the voluntary development and implementation of innovative pharmaceutical manufacturing and quality assurance technologies. Working with existing regulations, the Agency has developed a new, innovative process approach for helping the pharmaceutical industry address the technical and regulatory issues and questions anticipated during the introduction of such technologies. The scientific, risk-based framework outlined in this guidance, Process Analytical Technology or PAT, should help pharmaceutical manufacturers design, develop, and implement new efficient tools for use during product manufacture and quality assurance while maintaining or improving the current level of product quality assurance. The framework developed has two general components:

- A set of scientific principles and tools supporting innovation
- A new regulatory strategy for accommodating innovation

Among other things, the regulatory implementation strategy includes the creation of a PAT Team approach to CMC review and CGMP inspections and joint training and certification of PAT review and inspection staff. Together with the recommendations in this guidance, our new strategy should alleviate any concern manufacturers may have in introducing new technologies in a regulatory environment that encourages risk-based thinking. We ask manufacturers to use the PAT framework described in this guidance to develop and implement new pharmaceutical manufacturing and quality assurance technologies.

The PAT guidance has been written for a broad industry audience comprising different organizational units and scientific disciplines. Because it highlights technical and regulatory issues and questions anticipated during the introduction of such technologies, the PAT guidance is intended to be a typcial Agency guidance. It was developed through a collaborative effort involving CDER, the Center for Veterinary Medicine (CVM), and Office of Regulatory Affairs (ORA). Collaborative activities also included public discussions, PAT team building activities, joint training and certification, and research. An integral part of this process was the extensive public discussions at the PAT-Subcommittee of the ACPS, and the PAT-Subcommittee of the ACPS, as well as several scientific workshops. FDA plans to explore the possibility of expanding the scope of the PAT guidance to biological products.

**Focus Placed on the Science of Manufacturing**

The Manufacturing Science working group, which was established at the launch of the Pharmaceutical CGMPs for the 21st Century initiative, is involved in identifying efficient approaches for characterizing and controlling critical manufacturing process parameters and quality assurance. The primary focus of its activities is to use the knowledge of product and process development, scale-up, and production to help the agency incorporate the use of scientific and risk-based decisions. The Manufacturing Science working group will work with the PAT team in a number of efforts. First, efforts are underway to develop a broad regulatory strategy that ensures that existing application review and CGMP programs are based on sound state-of-the-art scientific and engineering knowledge. We hope the new regulatory strategy will encourage manufacturers to develop and implement the latest technologies in pharmaceutical manufacturing processes.

The PAT guidance, described above, emphasizes the importance of understanding processes. The guidance discusses a range of flexible options for qualifying and justifying new technologies, such as modern online process analyzers intended to measure and control physical and/or chemical attributes of materials to achieve real time release. By emphasizing the importance of understanding manufacturing processes, the Agency hopes to create win-win approaches for enhancing the use of product and process development knowledge throughout the life-cycle of a product. It is our goal to encourage industry to explore new, enabling technologies that may help the agency to develop new methods that allow the agency to address the scientific and regulatory requirements and issues anticipated during the introduction of such new technologies. We believe that the focus on process understanding will facilitate risk-based decisions and innovation by focusing on the use of PAT to create risk identification, management, and control methodologies.

Second, we have planned several scientific workshops domestically and overseas during the latter part of 2003 and the early part of 2004 for the purpose of exploring, identifying, and discussing innovative scientific risk-based approaches that will help us reach several of the goals of the Pharmaceutical CGMPs initiative.

Next, we are also announcing today that we will be collaborating with the National Science Foundation’s Center for Pharmaceutical Processing Research in support of the objectives of the PAT and Pharmaceutical CGMPs initiatives. This collaboration is also intended to expand the Agency’s scientific foundation in the area of innovative pharmaceutical manufacturing technology. We believe this collaboration will help the Agency develop and implement sound, science-based post-approval review and inspection strategies that are consistent with the recent emphasis on current and innovative systems for monitoring and controlling pharmaceutical manufacturing.

Finally, we have established a cooperative research and development agreement (CRADA) with Pfizer, Inc. to research chemical imaging applications in pharmaceutical manufacturing and quality assurance. Recent advances in chemical imaging technology make it possible to acquire and analyze high-resolution chemical images rapidly. Chemical imaging can now be applied to process monitoring and control. Such modern chemical-imaging tools can offer improved integration of the Preapproval and CGMP Inspection Programs.

**Emphasizing a Risk-Based Approach**

Even though the Pharmaceutical CGMPs initiative and related activities address risk-based approaches, certain aspects of the initiative focus primarily on implementing specific risk-based approaches. To ensure that a risk management approach is applied to allocating FDA inspectional resources, the Agency is developing risk-based site-specific inspection protocols. This model will be piloted for human drugs (CDER) in October 2004. The model will help the Agency predict where its inspections are most likely to achieve the greatest public health impact. The model will include risk factors relating to the facility (such as the compliance history) and to the type of drugs manufactured at the facility. The model will also include risk factors relating to the manufacturing processes and the level of process understanding.

The Agency also has developed action plans for the review and revision of field compliance programs to incorporate risk-based approaches to improve transparency and guide FDA investigators in conducting inspections. For example, the Agency will revise the sterile products compliance plan (for CDER products) upon finalization of the aseptic processing guidance. The Center for Veterinary Medicine (CVM) and ORA will be adopting a more systems based approach to allocating FDA inspectional resources and implementing new efficient tools for use during product manufacture and quality assurance while maintaining or improving the current level of product quality assurance.

To better understand which factors lead to superior manufacturing performance in the pharmaceutical industry, the Agency has signed a cooperative research and development agreement[14] with Professors Macher and Nickerson of Georgetown University and Washington University in St. Louis, respectively. The study they perform will help the Agency identify the factors that predict manufacturing performance to further refine our risk-based regulatory decisions and innovation as well as the use of appropriate risk identification, management, and control methodologies.

**Improved Integration of the Preapproval and CGMP Inspection Programs**

The FDA (USA) and the Center for Drug Evaluation and Research (CDER) signed a memorandum of understanding ([MOU]) on August 22, 2003, establishing the Pharmaceutical Inspectorate PI Frequently Asked Questions ([FAQ]). The PI is a staff of highly trained individuals within ORA who will devote most of their time to conducting human drug quality inspections on prescription drug manufacturers and other complex or high-risk pharmaceutical operations. The PI will also conduct preapproval inspections and may conduct or assist in investigations that require their expertise. The establishment of the PI

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will foster a close working relationship between the individuals in the field and CDER, working toward ensuring quality products. FDA expects to begin designating these individuals during fiscal year 2004. To serve as a member of the PI, an investigator will have to obtain and maintain a Level III Drug Certification. A Level III Drug Certification signifies that an individual has received extensive training in the pharmaceutical manufacturing process and on how those technologies are evaluated during an inspection. A Level III Drug Certification Board has been established to review certification packages, select candidates for membership into the PI, and develop, update, and maintain the curriculum for the Level III Drug Certification program.

We also plan to increase the use of product specialists to help ensure that submission reviews and CGMP inspections are coordinated and synergistic and that consistency in regulatory decisions is strengthened. Product specialists are individuals with specialized expertise in specific scientific/technical areas. These individuals will be reviewers, center commodity officers, or field inspectors. The use of specialists is already required, specifically within programs resident at the Center for Biologics Evaluation and Research (CBER) and also for the evolving technology-based PAT Initiative. Recognizing the value of interaction with other components of the CGMP initiative, the Product Specialist on Inspection Teams working group, which was established at the August 2002 launch of the Pharmaceutical cGMP initiative, is interacting and coordinating its activities with other working groups (see the diagram Potential Use of ‘Specialists’- An Evolving Team).[PDF].

The PAT Team approach for CMC review and CGMP inspections outlined in the PAT guidance will serve as a pilot for the use of specialists on inspections. The PAT Review and Inspection team is completing their training and certification program fall of 2003. The experience gained and lessons learned from PAT Team building and training programs will be used along with the experience gained from the Team Biologics program to structure further development of this program.

**Changed Procedures for Drug CGMP Warning Letters**

FDA has revised the regulatory procedure it uses for determining when to issue warning letters in response to noncompliance with current good manufacturing practice requirements. Since March 1, 2003, all proposals to issue a warning letter have been reviewed by the centers with product jurisdiction. The appropriate center will determine whether the letter can be issued. A single office authority for the approval of all letters will ensure that requirements are applied consistently.

A warning letter is an official notice to a regulated business establishment that objectionable conditions or practices have been identified in their operations, that corrections are expected, and that failure to correct the deficiencies may result in further FDA actions. Warning letters contain details of conditions and practices that are evaluated from data and other scientific information. Incorporating a central role in the process will ensure that adverse findings will be based on the best science available and will enhance communication and coordination between the field and centers and help identify possible program inconsistencies for resolution before the issuance of a warning letter. During the fall of 2003, an internal assessment will be performed to evaluate the new procedures.

**Continuing International Cooperation**

One of the guiding principles of this initiative has been international cooperation, including collaboration with other regulatory authorities, via the International Conference on Harmonisation (ICH) and other opportunities. Greater harmonization of international scientific standards on drug product quality will promote technological innovation for enhanced public health protection.

During the most recent ICH meeting, held in July 2003 in Brussels, agreement was reached on a common vision and approach for developing an international pharmaceutical regulatory framework. Several actions were outlined to implement this vision. An expert working group (EWG) was established to develop, which will incorporate elements of risk and quality by design throughout the life cycle of the product. A second EWG was established to better define the regulations by which risk management strategies will be integrated into decisions regarding product quality. FDA is included in both groups, and more generally, the Agency is working closely with the European Medicines Agency (EMEA) and Japan's Ministry of Health, Labor, and Welfare to further develop the ICH pharmaceutical quality system principles.

**Quality Management Systems**

The Agency has begun the complex process of designing an integrated Agency-wide, risk-based quality management system. As a first step toward enhancing the Agency's quality management system, the Steering Committee is developing a definition of quality in the context of pharmaceutical quality for the purposes of this initiative.

The original Quality Systems Working Group, formed at the launch of the initiative, was dedicated to enhancing the consistency and predictability of FDA's approach to production quality and safety assurance among our centers and field components. The original Quality Systems Working Group has been disbanded and replaced with new working groups (WGs): the Quality Systems Framework WG, the Quality Systems Guidance Development WG, and the CGMP Harmonization Analysis WG. Another working group has been established that will develop a mechanism similar to CBER's CGMP Notes that, consistent with good guidance practices, can quickly communicate FDA decisions and interpretations related to CGMPs and FDA inspectional findings to the public.

The Quality Systems Framework WG will be developing a framework that enhances and integrates the Agency's existing quality systems. This quality systems framework will be implemented in the involved centers and the field to ensure quality and consistency of reviews and inspections. To achieve greater consistency across the Agency, the framework will provide a common vocabulary and component description the Agency. The framework or model will include basic components, such as ensuring that there are process plans with written procedures; well-trained staff; record keeping and review; knowledge sharing and coordination and continuous process improvement. The working group expects to have a draft white paper for internal FDA review by October 31, 2003. The draft white paper will be made available for public comment by December 1, 2003.

The Quality Systems Guidance Development WG is developing new educational guidance documents to encourage the use of quality system principles. As a first step, the group is studying modern quality system principles from various sources so that the guidance that is developed can reflect the most modern principles of quality systems and quality management systems. The guidance will map these modern principles onto the CGMP requirements, reinforcing the very quality system principles they were founded on. The first guidance expected is to be released for comment by August 2004. An additional specific part of this component of the initiative, FDA expects to release a report in March 2004 on the contract that it awarded in March 2003 on Effective Quality System Practices. This project is intended to help improve the practices and policies of the FDA units involved in the regulation of pharmaceuticals by reviewing effective quality and regulatory system practices from other public or private organizations. As discussed in the next section, an educational series on this topic has been developed for FDA staff during the fall and winter 2003.

Finally, FDA has created a CGMP Harmonization Analysis working group that is analyzing internal and external GMP requirements, including those related to quality systems. Regulations to be reviewed include 21 CFR 210 and 211, European Union CGMPs, PIC/S[17] and other Agency-wide CGMP regulations. The differences between these regulations will be highlighted, and the Steering Committee will use an analysis of these differences to determine the value of revising 21 CFR 210 and 211. Opportunities for harmonization will be identified and prioritized. An interim report will be provided to the Steering Committee in November 2003. The working group expects to have a final analysis completed in May 2004.

**Training Related to the Initiative**

Six organizations have been identified that have expertise in quality systems and/or risk management approaches. They will be providing a series of presentations to FDA staff to share their lessons learned and approaches. This lecture series will provide FDA staff with current thinking in the quality systems and risk management areas and will offer FDA staff the opportunity to ask questions and learn about alternatives used by other organizations that may be applicable to this initiative.

In addition to the lecture series described above, a curriculum is being developed for investigators to become experts and potential members of the Pharmaceutical Inspectorate. The curriculum will include courses on risk management, LQI science underlying drug manufacturing, the FDA regulation of product quality, technology involved in manufacturing, enforcement processes, and team building. It is anticipated that the classroom courses in combination with on-the-job training will provide an enhanced science base for the inspectional personnel.

**Evaluation Planned**

We are continuing to refine our plans for evaluation of this initiative. In general, we expect to achieve gains of increasing quality or process efficiency. Our evaluation approach will include both quantitative and qualitative methods that are applicable to the different Agency activities and objectives included in this initiative.

Comments on the initiative and the implementation plan may be submitted to Docket number 03N-0059. However, comments on the 5 guidances should be submitted to their respective docket numbers.

1. Pharmaceutical inspection cooperation scheme (PIC/S).

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