

CHAPTER 56 - DRUG QUALITY ASSURANCE

SUBJECT: RADIOACTIVE DRUGS		IMPLEMENTATION DATE 09/11/2015
Revision Note: Program revised 09/11/2015 to update implementation date, completion date, organizational/procedural changes and program contacts.		COMPLETION DATE 09/11/2016
DATA REPORTING		
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES	
7356.002C	56002C	

FIELD REPORTING REQUIREMENTS

(Excluding Winchester Engineering and Analytical Center [WEAC])

Establishment Inspection Reports (EIRs) are to be created and filed electronically using the radioactive drug specific module in TurboEIR or replacement system that is accessible to both ORA and CDER.

For inspections of routine commercial manufacturing classified as Official Action Indicated (OAI) due to failure to comply with 21 CFR Part 210 and 211 Current Good Manufacturing Practice (CGMP) as they apply to radioactive drugs, submit advisory, administrative, or judicial action recommendations via MARCS-CMS in accordance with the Regulatory Procedures Manual (RPM).

Districts should immediately report significant issues according to current FACTS, Panorama and CMS procedures. This includes promptly filing and changing OAI notifications.

During an inspection, if you obtain information pertaining to inadequate adverse drug experience (ADE) reporting, unapproved drug issues, or post-approval reporting violations (application supplements, Field Alert Reports (FARs), etc.), report in accordance with directions provided in the applicable compliance programs and under separate captions in the EIR. Data system information about these inspectional activities should be reported under separate Program Assignment Codes (PACs).

Expansion of coverage under these programs into a CGMP inspection should be reported under this compliance program.

The Districts are requested to use this compliance program for all radioactive drug inspections.

WINCHESTER ENGINEERING AND ANALYTICAL CENTER (WEAC) REPORTING REQUIREMENTS

- A. Forward all worksheets to Home District with copy to CDER/Office of Product Quality (OPQ)/Office of Surveillance(OS).
- B. Send by Electronic Mail System (EMS) results of the examination of import samples to Home District.

PART I - BACKGROUND

History

Radioactive drugs are regulated by the FDA to the same extent that FDA regulates other drugs. With the exception of certain research uses of radioactive drugs (as specified in 21 CFR 361.1), all radiopharmaceuticals are considered to be new drugs and subject to the applicable provisions of the Federal Food, Drug, and Cosmetic Act and the drug regulations issued under Title 21 of the Code of Federal Regulations.

Definition

The term "radioactive drug" is defined in 21 CFR 310.3 (n) as any substance defined as a drug in the FD&C Act which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs which contain only trace quantities of naturally occurring radionuclides. The term "radioactive drug" includes a "radioactive biological product" as defined in 21 CFR 600.3 (ee).

Exception for Research Use

On July 25, 1975, the FDA established a special provision in 21 CFR 361.1 for certain research uses of radioactive drugs provided:

- the research was approved by an FDA Radioactive Drug Research Committee;
- the amount of active ingredient employed does not cause any clinically detectable pharmacological effect in humans;
- the amount of radioactive material administered to each subject is as low as is practicable; and,
- the radiation doses to the critical and target organs are within certain specified limits.

Under these conditions, radioactive drugs are generally recognized as safe and effective when administered to human research subjects during the course of a research project intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes, (i.e., to carry out a clinical trial).

Certain basic research studies, e.g., studies to determine whether a drug localizes in a particular organ or fluid space and to describe the kinetics of that localization, may have eventual therapeutic or diagnostic implications, but the initial studies are considered to be basic research within the meaning of this provision. Compliance Program #7348.809A, "Radioactive Drug Research Committees", covers the monitoring of radioactive drugs for these research uses.

PART II - IMPLEMENTATION

OBJECTIVES

*To provide guidance for conduction inspections of radioactive drug manufacturers to determine compliance with the Food, Drug and Cosmetic Act and the Current Good Manufacturing Practice Regulations (CGMP), Title 21, CFR Parts 210 and 211.

To initiate appropriate action against those manufacturers found to be out of compliance.

To obtain information on key practices, to identify practices which need correction or improvement, and to evaluate current good manufacturing practices in the radiopharmaceutical industry.*

Pre-marketing aspects of ' radioactive drug products are covered under Compliance Program #7346.832, "Pre-Approval Inspections." NDA methods validations for radioactive drugs, as for other drugs, will be performed by assignment.

PROGRAM MANAGEMENT INSTRUCTIONS

This program supplements CP #7356.002, "Drug Process Inspections," *and CP 7356.002A, "Sterile Drug Process Inspections" by providing specialized instructions for conducting inspections of radioactive drug manufacturing establishments.

Assignments for the collection of surveillance samples are issued under CP #7356.008, "Drug Product Surveillance."

Coverage

The term "radioactive drugs" includes radioactive biological products. A radioactive biological product is defined as a biological labeled or intended to be labeled with a radionuclide.

Radioactive drugs may be administered orally, by injection, or inhalation and may be either diagnostic or therapeutic.

1. A diagnostic radioactive drug functions in vivo as a radioactive tracer which is distributed throughout the body, or localized in particular organs or structures where the decay of the radioactive element is detected externally. It may also be used in in vitro clinical studies.

2. A therapeutic radioactive drug contains ' larger quantities of radioactivity for destruction of diseased cells or tissues.

THIS COMPLIANCE PROGRAM DOES NOT COVER RADIOACTIVE MEDICAL DEVICES. A radioactive medical device is a medical device as defined in Section 201(h) of the FD&C Act that contains or utilizes radioactive materials.

PART III - INSPECTIONALOPERATIONS

Districts will identify all manufacturers *(Attachment A deleted)* of radioactive drugs and radioactive biologics, determine whether they are registered under Section 510, and contact Division of Medical Imaging Products for verification of the firm's NDA and IND filings.

An enforcement policy for "nuclear pharmacies" has been stated in 49 FR 24949 (June 18, 1984).

A guideline has been issued (May 1984) which aids in distinguishing between those operations which are considered the practice of nuclear pharmacy, and those operations which constitute the practice of drug manufacturing.

Where an establishment has not registered as a drug manufacturer, but manufacturing is suspected, attempt to inspect, and forward the EIR to OPQ/OS for decision as to follow-up. The EIR should contain full documentation explaining why the establishment considers itself a pharmacy and why the district believes the establishment to be a drug manufacturer.

Districts will inspect each radioactive drug manufacturer *a minimum of once every two years on a surveillance basis* and will schedule compliance inspections as needed. *See instructions under CP 7356.002 or 7356.002A concerning frequency of full vs. abbreviated inspections.* -

Districts and the Division of Drug Quality Evaluation will issue assignments for collecting surveillance samples in coordination with Winchester Engineering and Analytical Center (WEAC) under CP #7356.008, "Drug Product Surveillance."

On assignment, the investigator team should review:

- All reference materials related to the type of products to be covered by the assignment.
- Pertinent manufacturing, analytical, and labeling sections of the IND or NDA, obtained if necessary from the OPQ/OS.
- Compendial requirements for USP/NF products.

- Current Good Manufacturing Practice Regulations, recognizing the differences between standard drug manufacturing procedures and the unique custom processing operations employed by the radioactive drug and radiobiologic manufacturers.
- 40 FR 31297 - 31314 (July 25, 1975) (attached)
- 41 FR 7747 (Feb. 20, 1976) (attached)
- 41 FR 35171 (Aug. 20, 1976) (attached)
- Nuclear Pharmacy Guideline (May 1984)

Investigators selected by the districts to undertake assignments made under this program will have completed the "FDA Advanced Training Course for Drug Inspectors, Radiopharmaceuticals."

Districts should consider using an investigator/chemist team in making an inspection of an establishment which has not been inspected previously. As complex instrumentation and methodology may be involved, chemists with education or training in nuclear science either from the district staff, WEAC, DDC, or DORDP will be made available. The district may wish to use the expertise of Regional Radiological Health personnel as members of the investigating team.

Because of the nature of radioactive drugs, most producers manufacture small batches based on anticipation of market needs, with production schedules established accordingly. This is particularly true where the radioactive nuclide has a short half-life and must be prepared, packaged, labeled, shipped, and used in a relatively short period of time, sometimes in a matter of hours.

All injectable radioactive drug products must comply with the normal requirements of safety, sterility, freedom from pyrogens, acceptable pH, and isotonicity. This is required by the United States Pharmacopeia with some qualifiers regarding sterility testing. In addition, 21 CFR 211.165(a) states, "where sterility and/or pyrogen testing are conducted on specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility or pyrogen testing, provided such testing is completed as soon as possible."

In cases where it is necessary to permit the radioactivity for short-lived nuclides to decay to a level allowing safe handling by laboratory personnel performing the test or so that the radioactivity will not compromise the test itself (e.g., injure the test animal), a delay in starting the test may be allowed; however, testing of each batch must be accomplished as soon as possible. Thus, investigators must realize that the production and quality control aspects of the formulation of these products achieves an importance which surpasses that employed in the marketing of the usual medicinal.

If the district requests additional personnel, they should notify the Division of Medical Products and Tobacco Program Operations (DMPTPO) with copy to DORDP (HFD-150), WEAC (HFR-1300) or DDA (HFH-300), as appropriate, at least three weeks in advance of the scheduled inspection so that a determination can be made as to the individuals to participate in a given inspection.

Agreement State Programs

The Nuclear Regulatory Commission (NRC) has authority to enter into agreements with State governments, with the State assuming regulatory responsibility over the receipt, possession, use, disposal, storage, and transfer of by-product source and specified quantities of special nuclear material in that State. The State's program must be compatible with the NRC program and the State must have the technical capability to protect public health and safety. In addition to Agreement States, other states may regulate the use of accelerator-produced or naturally-occurring radioactive materials which are not controlled by NRC.

Agreement State radiation control personnel are frequently expert in the detection of the improper use, manufacture, and safe-handling of radioactive materials. These State Inspectors have the training and calibrated equipment necessary to conduct radiation monitoring surveys, should it be deemed necessary, and can readily recognize radiation safety hazards.

The Directory of Personnel Responsible for Radiological Health Programs lists those professional personnel who administer the State and local government agencies.

Districts may wish to contact State and local radiation control agencies through their Regional Radiological Health Representative to obtain their cooperation. This may include their participation in establishment inspections as expert advisors on radiation safety, providing no information normally considered confidential (i.e., IND*/NDA*) is to be covered.

All firms that manufacture and/or produce reactor-produced radiopharmaceuticals operate under a license issued by the NRC or a regulatory agency of an Agreement State. Under the provisions of these licenses, each manufacturer shall have an individual designated as a Radiation Safety Officer (RSO) or radiation protection specialist. In addition, those areas where radioactive drugs are produced and stored shall be posted with a placard or sign bearing the radiation symbol and describing the radiation and/or contamination levels, and the precautions to be taken while in those areas (such as the wearing of protective clothing).

*Format

Inspections of radiopharmaceutical drug manufacturers will be performed under two compliance program guides, appropriate to the profile class of the dosage form being inspected.

Non-sterile dosage form radiopharmaceuticals will be inspected utilizing the instructions contained in Compliance Program #7356.002, Drug Process Inspections, supplemented by the instructions peculiar to radiopharmaceutical drug products contained in this Compliance Program.

Lyophilized and other sterile dosage form radiopharmaceuticals will be inspected utilizing Compliance Program 7356.002A, *Sterile Drug Process Inspections*, supplemented by the instructions specific to radiopharmaceutical drug products contained in this Compliance Program.

Inspections of radiopharmaceutical manufacturing firms will be performed as either Full Inspections or Abbreviated Inspections. The type of inspectional option to be selected will be determined following the selection options described in the Drug Process Compliance Program (7356-002) or *Sterile Drug Process Inspections* Compliance Program (7356.002A), as relevant to the product/profile class being covered. NOTE: Whether the Full or Abbreviated Inspection option is selected, the information requested under this (7356.002C) Radiopharmaceutical Compliance Program will be collected.*

INVESTIGATIONAL

Determine if establishment is registered under Section 510. Do not advise that they must register if they consider themselves a pharmacy. See 41 ER 7747 (Feb. 20, 1976).

A. Radiological Safety

Investigator teams assigned to inspections of radioactive drug manufacturers are expected to be familiar with radiation detection equipment and safety precautions as follows:

Personnel dosimeters - supplied by the ORA Radiological Safety Officer on a quarterly basis or as needed. Each badge is personally assigned and worn only by the designated investigator or chemist. It is required to be worn on the torso at all times during inspections or sampling assignments involving procedures of radioactive drugs.

District Radiological Safety Representatives are responsible for ordering and issuing dosimeters, and returning them to the ORA Radiological Safety Officer for processing, if necessary. When not in use, badges should be stored in a low radiation area away from sources of heat and moisture.

A self-reading dosimeter with a 0-200 mr range should also be carried during these assignments. It should be read before, during, and after the plant visit as an indicator of radiation exposure received for the period involved. The serial number and initial and final readings of self-reading dosimeters should be recorded for future reference.

Regional and District personnel now have available a personnel monitoring device which activates with a noise and light signal when a pre-set dose level is reached.

Handle these instruments with care as they may be discharged by shock if dropped.

Required protective clothing such as smocks, head and shoe covers, and gloves are usually provided by the firm's Radiation Safety Officer (RSO).

The investigator should exercise particular care in areas where iodine or technetium isotopes are being produced or processed to prevent an internal dose by inhalation of the iodine or from skin absorption of the technetium.

The firm's health physicist or RSO must accompany the investigator into controlled areas where radionuclide-sand radioactive drug products are processed, stored, or packaged. Avoid unnecessary handling of objects on the premises and follow all safety procedures required by the firm.

After leaving the firm's controlled area, remove all protective clothing by the "inside out" technique. Monitor yourself using the available monitoring equipment after washing hands, face, and other exposed areas. Leave protective clothing with the firm for disposal or laundering.

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Note: Each investigator is personally responsible for taking the necessary precautions to reduce exposure to ionizing radiation to the lowest possible level.

B. Raw Materials

Determine the adequacy of each firm's control procedures for handling raw materials and components. These would include logging the receipt, segregation, sampling, testing, and acceptance/release criteria, and storage for:

1. Product containers and their components (vials, generators, closures, syringes, needles, tubing, etc.).
2. Packaging materials.
3. Chemicals and other raw materials used in manufacturing, such as gelatin, colloidal sulfur, saline solution, buffers, radiochemicals, etc.

4. Radionuclides.

C. Manufacturing Controls

Report:

1. Steps taken by the firm to prevent the absorption of radionuclides on the walls of containers and preparation vessels. Document the use of any coating materials and the firm's validation that absorption does not occur and that delivery of the full dose is assured.
 2. Validated procedures utilized by the firm to prevent the carry over of by-products from chemical reactions to the finished product.
 3. The adequacy of pH controls during the processing of radioactive drugs where pH is critical to the purity or activity of the products, (e.g. iodine isotopes).
 4. The accuracy of in-process equipment and the adequacy of controls used to check whole bottle activity and/or container volume.
 5. Controls used to maintain the identity of components used in assembling kits, generators, etc.
 6. Any failure of the manufacturer to establish acceptable limits on theoretical and actual yields for small volume batches or radioactive drugs manufactured on special order. Audit representative batches manufactured before and during the inspections.
 7. Firm's procedures for monitoring the environment, personnel, glassware, equipment, and various stages in processing for evidence of contamination by radioactive materials.
 8. Methods for retesting stock solutions used in manufacturing. Are stock solutions checked for potency, impurities, and sterility where required? Is reconciliation performed on the use of stock solutions?
- D. Manufacturing Radioactive Drugs and Radiobiologic Products Which Meet Sterility Requirements (refer to CPG 7356.002A, Sterile Drug Process Inspections)

Report:

1. Procedures used to insure that processing equipment, glassware, final containers, and other components are free from chemical, microbial, pyrogenic, and radioactive contamination.

2. If re-use of stock solutions is encountered, the investigator should report fully the precautions taken by the firm.

*Some portions deleted from this section due to duplication under the Sterile Drug Process Compliance Program.

E. Generator Systems

The use of nuclide generators, such as the Mo 99m/Tc 99m generator, has increased in recent years and they pose special problems. When encountered during an inspection, report the following information:

1. Quality control procedures used in the assembly, testing and re-use of the generator-system regarding the following areas:
 - Assay
 - Calibration
 - Sterility
 - Pyrogens
 - pH
 - Contaminants (radioactive and non-radioactive)
 - Daily elution pattern
2. Any use of bacteriostats in the preparation of eluting solutions.
3. Instructions provided the user as to the assembly, operation and maintenance of sterility.
4. Details of any training program designed for hospital personnel authorized to use generator systems.
5. Determine the manufacturer of the generator and the source of the radioactive materials within it.

F. Packaging and Labeling

1. Report procedures for storing, issuing and accounting for labeling and insert materials. Give particular attention to small custom batches.
2. Determine the accuracy of the labeling statement for volume, chemical content, total activity per unit volume at date and time of calibration. Report any difference between actual and theoretical activity at date and time of calibration by the firm in comparison to the labeled activity.

3. A determination should be made that the kit label and the label of each component of the kit bear the same expiration date which is based on the component with the earliest expiration date. The procedure used for assuring a single and valid expiration date for multi-component kits should be reviewed.
4. Examples of labeling are to be submitted to CDER. CDER will review storage precautions, directions for use, expiration date, and any special limitation statements on product labeling for conformance with compendial and/or NDA requirements.
5. Determine if in-process content uniformity checks are made on capsules and if liquids are examined for fill of container and total activity.
6. Report firm's procedures for identifying components (kits, syringes, dilution bottles, etc.) packaged with the radioactive drug, or shipped under separate order.

G. Analytical Controls

Report:

1. Any microbiological, chemical, and pyrogen tests performed on water intended for parenteral preparations.
2. Tests to establish the potency and purity of reagents and materials intended for tagging (e.g., vitamin B 12, colloidal sulfur, gelatin, isotonic saline solution, etc.).
3. Any analysis of isotopes for radionuclide identification, and purity, radiochemical identification, purity, and activity.
4. Sterility and/or pyrogen tests performed on presterilized components, intermediates, and raw materials used in manufacturing.
5. Capsule preparations for content uniformity, chemical content, and activity.

6. Tests performed on finished radioactive drugs and biologicals as follows:

- Chemical purity
- Radiochemical purity
- Radionuclidic identification and/or purity
- Total radioactivity (assay or radioassay)
- Sterility (USP requires that sterility tests be initiated prior to shipment)
- pH and particulate matter
- Fill of container and packaging requirements
- Pyrogens (where required for injections)
- Toxicity
- Biodistribution

Note: Refer to NDA and/or compendial monograph for specific analytical requirements.

7. Determine if analytical procedures follow NDA commitments and/or compendial requirements.
8. The date and source of analytical standards.
9. Review the frequency and methods for standardizing the house standards and stock solutions.
10. Current stability testing programs. Does the program data support firm's expiration dating system?
11. During the first inspection, all instruments used in control operations should be listed by name and model number. Any changes in instrumentation should be noted on successive inspections.
12. Method and frequency of calibration of all quality control instrumentation.
13. Determine the actual testing frequency for each test.

H. Complaints

1. Check complaint files for drug defects, drug administration problems, adverse experience reports, and product rejections.
2. Report firm's response to complaints and the dispositions of any returned goods.

I. Products For Sampling

Identify products from firm's price list or catalog that should receive analytical coverage based on inspectional findings, recalls, complaints, etc. This list will be used by the OPQ/OS in the selection of samples for drug surveillance requests under CP #7356.008, "Drug Product Surveillance."

When sampling is necessary to document violations, collect samples of products from packaged stock ready for shipment. Select products with half-lives sufficiently long so that time necessary for collecting shipment and analysis is not a limiting factor.

J. Catalogs and Labeling

1. Obtain I copy of the firm's latest catalog or price list. Current copies or revisions should be marked for referral to OPQ/OS.
2. Obtain representative labeling of products inspected and attach as exhibits.

SAMPLE COLLECTION

Requests to collect radioactive drug surveillance samples, both District-initiated and Center-initiated will be issued under CP #7356.008, "Drug Product Surveillance." Compliance samples will be collected at District discretion or by direction of DDQE. Because the labs must schedule this workload and remain within NRC radioactive material license possession limits for the amount of radioactive material which may be on hand at any time, the Districts will coordinate sampling with WEAC prior to collection.

Where necessary to document Good Manufacturing Practice Regulations (GMP) deviations and other violations of the Act, official samples should be collected in the following manner.

A. Collection

1. Collect documentary samples of raw materials, in-process radioactive drugs, labeling, etc., to document GMP deviations where physical samples are impractical.
2. Long-lived radionuclides may be collected from plant stocks or from batches manufactured during the time of inspection and after release by firm's quality control department.

3. Many products, especially those of short-lived nuclides, are manufactured on order only. In such cases it will be necessary to obtain samples from products being packaged (filled) during a plant visit. Such sampling must not prevent the manufacturer from meeting customer orders. Arrange with the firm to determine the date of its next regular production of the required products. If the timing is satisfactory to the laboratory, arrange to have an additional amount of a batch filled in order to provide for an FDA sample. Arrange with the firm for the necessary transportation of the product so that the sample will be delivered to the FDA laboratory in sufficient time for analysis. The investigator should be present during the production in order to observe as closely as possible the labeling and filling operation of the product. Select required units at random after the product has been filled and labeled.

Caution: Do not request the firm to manufacture or fill a batch for the sole purpose of obtaining a sample.

4. If during an inspection, GMP deviations which are related to potency, sterility, pyrogen problems or other contamination are encountered, official samples should be collected. Contact OPQ/OS for assistance, if necessary.

B. Sample Size:

1. Collect a minimum of 20 capsules for Sodium iodide 1 131 Capsules, Cyanocobalamin Co 57 Capsules, Cyanocobalamin Co 60 Capsules and any other product where content uniformity is a compendial or NDA requirement.
2. Collect the smallest commercial unit offered for sale in the median dosage range when sampling oral preparations and sterile injections.
3. If plant conditions indicate the need for sterility, pyrogen, or toxicity tests, contact the OPQ/OS for sampling instructions and sample size requirements.

C. Sampling Instructions

1. Do not handle the immediate container of any radioactive products.
2. Plant personnel should place the immediate container in a suitable protective container in accordance with the establishment's radioactive materials license and DOT shipping regulations.

3. Officially seal the protective container before it is placed in the final shipping container. It is not necessary to further identify the protective container or to attach a FDA-525 to the shipping container.
4. Obtain a copy of shipping records and product labeling for attachment to your C/R.
5. Request the manufacturer to ship your sample via their normal mode of transportation to the laboratory designated by assignment:

U.S. Food & Drug Administration
Winchester Engineering and Analytical Center (HFR-NE490)
ATTN: Supervisory Chemist
109 Holton Street
Winchester, Massachusetts 01890

6. Report details concerning the product and shipment by telephone to WEAC as follows:
 - a) C/R number and date sampled.
 - b) Name of product, activity, time of filling, expiration date batch code, and number and size of unit(s) collected.
 - c) Name and address of manufacturer.
 - d) Reason for collection and analyses required.
 - e) Carrier and method of transportation, airbill number (when appropriate).
 - f) Shipping date and expected date and time of arrival.
 - g) Pertinent information from shipping records.
7. Confirm by EMS the information provided by telephone to the appropriate Radiological Safety Officer or to the RAL Supervisory Chemist, WEAC (HER-NE490) for samples shipped to the Winchester laboratory.
8. Prepare a Collection Report as soon as possible and send the Sample Record Copy 4 (salmon) to the analyzing laboratory. Flag the C/R "Radioactive Drug or Radioactive Biological Sample". Forward a copy of the C/R to OPQ/OS. Attach a copy of shipping records and labeling to your original (white) C/R.
9. Under the Remarks section of your C/R report:
 - a) Potency (radioactivity) and the exact time and date the Potency determination was made at the manufacturer or repacker.
 - b) Any unusual or suspected practices which might affect the product.

IMPORTS

The Administration cannot, at present, readily determine the extent of importation of radioactive drugs. In order to provide coverage, Districts will alert Customs and other local officials to advise FDA of all imports and will maintain surveillance by review of import entry forms, invoices, etc. When shipments of sufficient size, frequency and suitable half-life are encountered, consider collection of samples under the District-initiated portion of the Drug Product Surveillance CP. Consult with the OPQ/OS and WEAC before attempting such sampling.

Inspection of foreign manufacturers will be coordinated by the Division of Medical Products and Tobacco Inspections (DMPTI).

Considerations will be given to the district's ability to sample at port of entry or at consignee's location (handling and shipping), nature of product, size of lot, ability of laboratory to analyze, etc.

Release individual shipments being sent to physicians and hospitals after determining that the drugs meet the requirements of 21 CFR 361.1 or are new drugs covered by approved NDAs.

PART IV - ANALYTICAL

Winchester Engineering and Analytical Center (WEAC) will analyze compliance radioactive drug samples sent to them under this program. It will assist in the inspection of these firms and collect samples. WEAC will validate methodology of NDA's upon request of Division of Imaging Products (DIP).

WEAC will examine samples collected. Official and non-official preparations will be tested by appropriate methodology which will include, but not be limited to, the following basic analytical criteria:

- Radionuclide identity - demonstrating that the principal radionuclide is the one it is declared to be.
- Radionuclide purity - identifying and quantifying radionuclide contaminants.
- Radiochemical identity - demonstrating that the principal chemical form of the radionuclide is the one it is declared to be.
- Radiochemical purity - showing the fraction of the principal radionuclide which is in the specified chemical form.
- Radionuclide assay - measuring the radioactivity of the principal radionuclide and comparing it with the label declaration.
- Non-radioactive chemical tests - establishing identity, purity, and strength of non-radioactive components.
- Sterility or pyrogenicity - determinations, when necessary, will be performed by WEAC.
- Biological distribution (Biological Efficacy), when necessary, will be accomplished through sample preparation and animal work.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

In most cases, seizure or recall of small batches of short-lived radioactive drug products will not be feasible because they are dispensed so quickly. NAF and regulatory letters, injections and prosecution are other options. Withdrawal of an NDA or a supplemental NDA is an additional option; however, it has only been used on very rare occasions.

The Home District will consider all of the inspectional, analytical, administrative, voluntary and regulatory follow-up options available when a violative situation is encountered. The district will select the most appropriate option or combination of options. Appropriate regulatory action will be recommended to the OPQ/OS.

Refer to Part V of the Drug Process Inspections Compliance Program 7356.002 for general information on regulatory procedures.

PART VI - REFERENCES, ATTACHMENTS AND PROGRAM CONTACTS

REFERENCES

1. Radiation Safety Handbook for Ionizing and Non-Ionizing Radiation, DHEW Publication (FDA) 77-8007 *(Current Revision)*
2. Safe Handling of Radioactive Materials, Handbook 92, U.S. Department of Commerce, National Bureau of Standards, NCRP Report No. 2 (1964)
3. Remington's Pharmaceutical Sciences, *Current Edition*
4. Briner, W.H., "The Preparation of Radioactive Chemicals for Clinical Use," American J. Hospital Pharm., 20, 553-561 (1963)
5. USP/NF (Current Edition)
6. Radioactive Pharmaceuticals, USAEC. Division of Technical Information Extension, Oak Ridge, TN, April, 1966, AEC Symposium Series No. 6 CONF-651111. ,
7. Cliggett, P.A. and Brown, J.M. "Assays of Radioactive Materials for Use in Patients - A Five Year Study", Journal of Nuclear Medicine, 9, 236-240 (1967)
8. Radioisotope Directory, 2nd Edition (1971), Supplement to Dec. 1970 Nuclear News, American Nuclear Society, Hillside, IL 60521
9. "Radiation Monitoring", AEC, Division of Technical Information Extension, P.O. Box 62, Oak Ridge, TN 37830
10. AMA Drug Evaluation, Current Edition, American Medical Association, Chicago, IL
11. Analytical Control of Radiopharmaceuticals, Proceedings of a Panel, Vienna, 7-11 July (1969); International Atomic Energy Agency, Vienna, (1970). Panel Proceedings Series. Unipub, Inc., P.O. Box 443, New York, NY 10016
12. "Directory of Personnel Responsible for Radiological Health Programs", Conference of Radiation Control Program Directors, Inc., 71 Fountain Place, Frankfort, KY 40601, published annually.
13. "Radiopharmaceuticals" (1975) Society of Nuclear Medicine, New York

14. Quality Control in Nuclear Medicine; Buck A. Rhodes (1977)
15. Federal Register of June 18, 1984 - 24949-50
- *16. Inspection Technical Guide, "Radiation Protection Terminology,"
date 5/15/86, Number 44.*
- *17. Regulatory Procedure Manual, Part 8*.

ATTACHMENTS:

- A. Radioactive New Drugs and Radioactive Biologics - Termination of
Exceptions 40 FR 31297-31313 (July 25, 1975)

Radioactive Drugs, Including Biological Products - Notice to
Nuclear Pharmacies 40 FR 31314 (July 25, 1975)
- B. Radioactive New Drugs and Radioactive Biologics; Extension of
Time for Continued Commercial Distribution
40 FR 7747 (Feb.20,1976)
- C. Radioactive New Drugs and Radioactive Biologics; Extension of
Time for Continued Commercial Distribution 41 FR 35171 (August
20, 1976)

CONTACTS

A. ORA

Office of Operations (OO)/Office of Medical Products and Tobacco
Operations (OMPTO):

ORAHQDrugInspectionPOC@fda.hhs.gov

ORA/ORO/OR

S

Telephone: 301-796-6600

B. CDER

1. **CGMP or any Quality-Related Policy Questions**

For CGMP or any quality-related policy question, technical or
scientific questions or information needs, including questions about
this program, please send an email to the following address and it
will be handled as a top priority:

CDER-OPQ-Inquiries@fda.hhs.gov

Enforcement-Related Guidance or Policy

For enforcement-related guidance or policy, including evidence need and sufficiency, citations, and case evaluation/recommendation advice, please send an email to the following address and it will be handled as a top priority:

CDER OMQ Compliance Policy: CDEROMQCompliance@fda.hhs.gov

Labeling Requirements and Policies

Office of Unapproved Drugs and Labeling Compliance, see intranet home page for contacts
[CDER | Office of Compliance | Office of Unapproved Drugs and Labeling Compliance]

Registration and Drug Listing Requirements

CDER Office of Compliance, see "CDER: Who's the Lead" intranet page for contacts
[CDER | Office of Communications | CDER: Who's the Lead]

2. To report shipments to laboratories and for problems with sample collections and analyses, size, etc.:
 - a. Winchester Engineering and Analytical Center
ORA *(HFR-NE490)*
Telephone: FTS 839-8711 (area code 617)
 - b. CDER/OPQ/OS
CDERSURVEILLANCE@fda.hhs.gov

3. For problems concerning radiation safety and protection:

Regional Radiological Health Representative,
or if not available:

Edmond Baratta, Radiation Safety Officer
Telephone 781-756-9742
Edmond.Baratta@fda.hhs.gov

PART VII - CENTER RESPONSIBILITIES

The OPQ/OS will review all Establishment Inspection Reports forwarded by the Districts. Districts will keep the OPQ/OS advised of their plans for surveillance and compliance sampling. This Division will evaluate all laboratory findings.

CDER will review storage precautions, directions for use, expiration date, and any special limitation statements for product labeling for conformance with compendial and/or NDA requirements.

Program
Evaluation

The OPQ/OS will periodically evaluate this activity. Evaluations will be made generally available.

ED: Attachment A is a copy of the Federal register: not included in scanning.

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PART II

DEPARTMENT OF
HEALTH,
EDUCATION, AND
WELFARE

Food and Drug Administration

RADIOACTIVE DRUGS
AND RADIOACTIVE
BIOLOGICAL PRODUCTS

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