FDA PUBLIC WORKSHOP
ABBREVIATED NEW DRUG APPLICATIONS
POSITRON EMISSION TOMOGRAPHY
PARKLAWN BUILDING - ROCKVILLE, MD
APRIL 28, 1997

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AGENDA
FDA PUBLIC WORKSHOP
ABBREVIATED NEW DRUG APPLICATIONS;
POSITRON EMISSION TOMOGRAPHY RADIOPHARMACEUTICALS
PARKLAWN BUILDING - ROCKVILLE, MD
APRIL 28, 1997

Moderator - Gordon Johnston

8:00-8:10 a.m.	Opening Remarks	*Jane Axelrad*
8:10-9:00 a.m.	ANDA Regulatory Requirements	*Peter Rickman*
9:00-9:30 a.m.	Panel Discussion *Peter Rickman* *John Grace* *Cecelia Parise* *Jerry Phillips* *Vilayet Sayeed*	
9:30-9:45 a.m.	Drug Registration and Listing System	*Gary Anderson*
9:45-10:00 a.m.	Discussion	
10:00-10:15 a.m.	BREAK	
10:15-11:00 a.m.	Chemistry, Manufacturing and Controls	*Eric Sheinin*
11:00-12:00 p.m.	Panel Discussion *Eric Sheinin* *Bonnie Dunn* *Ravi Kasliwal* *Eldon Leutzinger* *Milagros Salazar* *Vilayet Sayeed*	
12:00-1:30 p.m.	LUNCH	

1:30-2:30 p.m.	CGMP Regulations/ Inspection Issues	*R.K. Leedham*
2:30-3:30 p.m.	Panel Discussion *R.K. Leedham* *James Finn* *Milagros Salazar* *Michael Verdi*	
3:30-3:45 p.m.	BREAK	
3:45-4:15 p.m.	Sterility Assurance	*David Hussong*
4:15-4:30 p.m.	Panel Discussion *David Hussong* *Peter Cooney* *Ken Muhvich*	
4:30-4:45 p.m.	Radioactive Drug Research Committee (RDRC)	*Brian Pendleton*
4:45-5:00 p.m.	Closing Remarks	*Gordon Johnston*

PET Steering Committee

Policy
Jane Axelrad, Chair
Supported by:
Khyati Roberts
Nancy Derr
Tom Kuchenberg
Brian Pendleton

Office of Compliance
Betty Jones
R.K. Leedham (Alternate)

Office of Review Management
James Cheever

Office of Generic Drugs
Gordon Johnston
Cecelia Parise (Alternate)

Office of New Drug Chemistry
Bonnie Dunn
Susan Lange

Office of the Chief Counsel
David Horowitz

Office of Regulatory Affairs
James Dunnie

BIOGRAPHICAL SKETCHES OF WORKSHOP PARTICIPANTS

Name: **Jane Axelrad**
Degree: **J.D.**
Position Title: **Associate Director for Policy**
Organization: **FDA/CDER**
Phone Number: **301-594-5400**

Responsibilities: Responsible for the development of all regulations and policies affecting the Center for Drug Evaluation and Research. Coordinator for user fee billing activities.

Experience: Worked in the Office of Generic Drugs on a variety of issues including generic drug monographs. Executive Director of the Blue Ribbon Committee on Generic Medicines, a panel formed by the Generic Pharmaceutical Industry Association to conduct an independent examination of the generic drug industry and the Food and Drug Administration's generic drug approval process. Has also held a variety of other legal and program positions at the Nuclear Regulatory Commission and the Environmental Protection Agency.

Name: **Peter H. Cooney**
Degree: **Ph.D., Microbiology**
Position Title: **Chief, Microbiology Staff**
Organization: **FDA/CDER/ONDC**
Phone Number: **301-443-5818**

Responsibilities: As Chief of the Microbiology Staff, is the lead product quality microbiologist in CDER and is responsible for policy development as well as coordination of policy in the review of applications concerning sterilization, sterility assurance, and microbiological quality of drug products.

Name: **Bonnie B. Dunn**
Degree: **Ph.D., Chemistry**
Position Title: **Deputy Director, DNDCIII; PET Expert**
Organization: **FDA/CDER/OPS/ONDC/DNDCIII**
Phone Number: **301-827-2003**

Responsibilities: Administrative and program management in the Division of New Drug Chemistry III. Provide expert advice in the area of chemistry, manufacturing and controls for PET drug products.

Experience: Adjunct Professor in Positron Emission Tomography Facility a the Vanderbilt University Medical Center, Vanderbilt University School of Medicine, Department of Radiology and Radiological Sciences, Nashville, TN, 1995; 1996; Chief of the Quality Assurance/Regulatory Affairs Section for all routine radiopharmaceuticals which were prepared with cyclotron produced radionuclides by the Radiochemistry Section of Institutes of Health, Clinical Center, Bethesda, MD, 1984-1993; Publications include research and development for a variety of radiopharmaceuticals.

Name: **James L. Finn**
Degree: **B.S., Environmental Science**
Position Title: **Consumer Safety Officer, Resident-in-Charge**
Organization: **FDA/Chicago District/Peoria, IL**
Phone Number: **309-671-7293**

Responsibilities: As a Resident Investigator, responsible for all activities of the FDA within a 21 county area of central Illinois.

Experience: Performs inspections of regulated firms, including The Downstate Clinical PET Center at the Methodist Center in Peoria, IL, the first PET center to obtain approval to market the PET pharmaceutical, FDG-F18.

Name: **John Grace**
Position Title: **Team Leader, Labeling Review Branch**
Organization: **OGD/DLPS/LRB**
Phone Number: **301-827-5846**

Responsibilities: Responsible for oversight of the review of labeling for all ANDAs as well as responding to general questions related to labeling requirements for generic drug applications.

Name: **David Hussong**
Degree: **Ph.D., Microbiology**
Position Title: **Regulatory Scientist**
Organization: **OPS/ONDC/Microbiology Staff**
Phone Number: **301-443-3560**

Responsibilities: Primary review of sterility assurance and microbiological quality attributes of drug products described in applications, as well as preparation of regulatory communications for industry, professional associations and regulators.

Experience: Is a Commissioned Officer of the U.S. Public Health Service. He is a microbiologist experienced in environmental bacteriology and immunology. He has represented the FDA in collaboration with the International Atomic Energy Agency on diagnosis of mycobacterial meningitis, and was an invited speaker at the International Seminar Series on Nuclear Techniques in Communicable and Parasitic Infections (1988: Bombay, India).

Name: **Gordon Johnston**
Degree: **M.S., R.Ph.**
Position Title: **Deputy Director, OGD**
Organization: **FDA/OGD**
Phone Number: **301-827-5845**

Responsibilities: Management, operations and policy oversight of the Office of Generic Drugs.

Name: **Ravindra K. Kasliwal**
Degrees: **Ph.D., Medicinal Chemistry, M.Sc., Organic Chemistry**
Position Title: **Review Chemist**
Organization: **ONDC/DMIRDP**

Responsibilities: Review of chemistry, manufacturing, controls and related information submitted in investigational and marketing drug applications for radiopharmaceuticals.

Experience: Joined the FDA in April 1994 as a Review Chemist in the Division of Medical Imaging and Radiopharmaceutical Drug Products. Before coming to FDA, was an Assistant Professor of Radiology at the University of Colorado Health Sciences Center, and was responsible for the University Hospital's radiopharmacy operation. Prior to that, performed basic research in radiopharmaceuticals at the University of Pennsylvania. Dr. Kasliwal has experience in both basic and clinical areas of diagnostic as well as therapeutic radiopharmaceuticals, research experience in anticancer drugs and steroid compounds.

Name: **Robert K. Leedham, Jr.**
Degree: **B.S., Pharmacy; M.S., Nuclear Pharmacy; Board Certified Nuclear Pharmacist**
Position Title: **Regulatory Operations Officer**
Organization: **CDER/OC/DSI**
Phone Number: **301-594-1026**

Responsibilities: Coordinates and manages various initiatives related to PET drug products for the CDER Office of Compliance. Serves as the lead individual, in establishing, coordinating, and integrating policy and guidance for the Office of Compliance, with the CDER Associate Director for Policy, Office of Review Management and the Office of Generic Drugs, on issues including manufacturing, registration and drug listing, prescription and product surveillance, and scientific investigations related to PET drug products. Responsible for supervising and managing the compliance program for the Radioactive Drug Research Committee.

Name: **Eldon E. Leutzinger**
Degree: **Ph.D., Chemistry**
Position Title: **Chemistry Team Leader**
Organization: **OPS/ONDC/DNCDII**
Phone Number: **301-443-1560**

Responsibilities: Provides leadership to the Imaging/Radiopharmaceutical Chemistry Team, co-located with the Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160). Responsible for coordination and management of the chemistry team, and for maintenance of scientific quality and performance standards in the review of medical imaging submissions, including uniformity and consistency with existent policies and procedures governing chemistry review.

Experience: Eight years with the Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160). Previous to coming to the FDA, was Senior Research Chemist in the Department of Nuclear Medicine, University of Connecticut health

Center, Farmington, Connecticut, 1982-1989. Responsible for the development of chemistry R&D programs for radio labeling of drug candidates for potential use in nuclear medicine diagnostic procedures and radiotherapy.

Name: **Kenneth Muhvich**
Degree: **Ph.D., Microbiology**
Position Title: **Review Microbiologist**
Organization: **FDA/OGD**
Phone Number: **301-827-5848**

Responsibilities: Primary review of sterility assurance and microbiological attributes of drug products described in applications, as well as preparation of regulatory communications for industry, professional associations and regulators.

Name: **Cecilia Parise**
Degree: **R.Ph., B.S., Pharmacology**
Position Title: **Consumer Safety Officer**
Organization: **CDER/OGD/RSB/DLPS**
Phone Number: **301-827-5862**

Responsibilities: Includes reviewing initial submissions of ANDA's for completeness and acceptability, providing answers to general questions regarding regulatory requirements for ANDA's, providing guidance to industry regarding the Office of Generic Drugs's inactive ingredient policy. Additional responsibilities include ANDA Suitability Petitions, and tracking consults sent by the Office of Generic Drugs to other reviewing divisions.

Name: **Brian L. Pendleton**
Degrees: **M.A., J.D.**
Position Title: **Regulatory Counsel**
Organization: **CDER/OCD/RPS**
Phone Number: **301-594-5649**

Responsibilities: Drafting proposed and final rules on drug regulations, drafting responses to citizen petitions on drug matters, reviewing and editing CDER guidance documents.

Name: **Jerry Phillips**
Degree: **B.S., Pharmacy**
Position: **Director, Division of Labeling and Program Support**
Organization: **FDA/OGD**
Phone Number: **301-827-5845**

Responsibilities: Responsible for the labeling and regulatory oversight of all generic drug products within the Office of Generic Drugs.

Experience: 23 years of clinical pharmacy and regulatory experience with the U.S. Public Health Service. This includes the past 8 years with the Office of Generic Drugs.

Name: **Peter Rickman**
Degree: **B.S., Chemistry/Biology**
Position Title: **Chief, Regulatory Support Branch, Office of Generic Drugs**
Organization: **FDA/CDER/OGD**
Phone Number: **301-827-5846**

Responsibilities: Responsible for oversight of filing Abbreviated New Drug Applications as well as responding to general questions related to regulatory requirements for generic drug application.

Name: **Vilayat A. Sayeed**
Degree: **Ph.D. Chemistry**
Position Title: **Team Leader, Branch 1**
Organization: **OGD**
Phone Number: **301-827-5848**

Responsibilities: Responsible for the oversight of the Chemistry, Manufacturing and Controls of all ANDA's in the branch, and also responsible for the resolution of technical issues raised in the reviews.

Name: **Milagros Salazar-Driver**
Degree: **M.S., Radiopharmacy ; Ph.D., Radiological Sciences**
Position Title: **Review Chemist**
Organization: **FDA/CDER/OPS/ONDC/DMIRDP**
Phone Number: **301-443-1560**

Responsibilities: Include: evaluation of the chemistry information and data of NDAs, ANDAs INDs, and supplemental new drug applications. These evaluations involve the review of chemistry, manufacturing, controls, stability, bioavailability/bioequivalence, technical aspects of labeling and environmental impact. Other regulatory responsibilities include policy formulation accomplished through FDA guidelines and committees. Specializes in radiopharmaceutical products. Reviewed the first approved NDA for F-18 FDG Injection, and participated in the creation of both CGMP and CMC issues on PET drug applications guidelines. Participated in the first FDA-ICP Training Workshop on CGMPs for PET radiopharmaceuticals in 1995.

Experience: 10 years of professional experience in radiopharmaceutical chemistry, hospital and centralized radiopharmacy in two countries: USA (Oakland Regional Naval Medical Center, Pharmatopes, Inc. - now Syncor Inc., George Washington Medical Center), and Mexico (National Institute of Cardiology). Experienced in synthesis, characterization and selection of iminodiacetic acid ligands for hepatobiliary imaging with Tc-99m; manufacture and formulation of kits for Tc-99m labeling; and dispensing radiopharmaceuticals with all radionuclides used in the routine Nuclear Medicine procedures. Also, bifunctional derivatization of proteins and antibodies for labeling with In-111 indium chloride and their biodistribution studies in animals.

Name: **Eric B. Sheinin**
Degree: **Ph.D., Chemistry**
Position Title: **Director, ONDC**
Organization: **FDA/CDER/OPS/ONDC**
Phone Number: **301-443-0260**

Responsibilities: As Director of the Office of New Drug Chemistry, has administrative and management responsibility for the review of the chemistry, manufacturing, and controls (CMC) and microbiology portions of new drug applications, investigational new drug applications, and supplements and amendments submitted to these applications.

Name: **Michael J. Verdi**
Degree: **B.S.**
Position Title: **Compliance Officer**
Organization: **FDA/CDER/OC**
Phone Number: **301-594-0095**

Responsibilities: Deals with Domestic and Foreign Drug Approvals involving Current Good Manufacturing Practice operations.

Experience: Former FDA field investigator with duties from 1977 to 1987 in the Richmond, Virginia Resident Post and from 1987 to 1995 in the Des Moines, Iowa Resident Post.

ACRONYM DEFINITIONS

FDA:	Food and Drug Administration
CDER:	Center for Drug Evaluation and Research
ONDC:	Office of New Drug Chemistry
OPS:	Office of Pharmaceutical Science
DNDC:	Division of New Drug Chemistry
OGD:	Office of Generic Drugs
DLPS:	Division of Labeling and Program Support
LRB:	Labeling Review Branch
DMIRDP:	Division of Medical Imaging and Radiopharmaceutical Drug Products
OC:	Office of Compliance
DSI:	Division of Scientific Investigations
RSB:	Regulatory Support Branch
OCD:	Office of the Center Director
RPS:	Regulatory Policy Staff

Guidance for Industry

Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 1997

OGD 1

Guidance for Industry

Organization of an Abbreviated New Drug Application and an Abbreviated Antibiotic Application

Additional Copies are available from:

The Drug Information Branch
Division of Communications Management, CDER, FDA, HFD-210
5600 Fishers Lane, Rockville MD 20857
(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 1997

OGD 1

GUIDANCE FOR INDUSTRY[1]

ORGANIZATION OF AN ABBREVIATED NEW DRUG APPLICATION AND AN ABBREVIATED ANTIBIOTIC APPLICATION

I. INTRODUCTION

This guidance describes the recommended organization of abbreviated new drug applications (ANDAs) and abbreviated antibiotic applications (AADAs) and related submissions. Some ANDA and AADA submissions are difficult to review because they are complex, voluminous, or poorly organized. An application submitted with the proper jacket, organized with a clear table of contents and corresponding tabs, and with correct pagination makes the review process easier and more efficient. This guide summarizes one way an application can be organized that will be acceptable to the Food and Drug Administration (FDA). This guidance document replaces the Office of Generic Drugs Policy and Procedure Guide 30-91.

II. DEFINITIONS

A. Abbreviated Application

An application described under 21 CFR § 314.94, including all amendments and supplements to the application. The term applies to both abbreviated new drug applications and abbreviated antibiotic applications.

B. Archival Copy

A complete copy of the an abbreviated application intended to serve as the official reference source for the Agency.

C. Field Copy

A duplicate of the archival copy to be submitted to the applicant's home FDA District Office.

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[1]This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the organization of an abbreviated application. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

D. Review Copy

A duplicate of the archival copy for use by Agency reviewers.

III. POLICY

A. Archival, Review, and Field Copy

An ANDA and AADA applicant should submit archival, review, and field copies of the application in English.

The archival copy is a complete copy of an application and is intended to serve as the official reference source for the Agency. After an application is approved, the archival copy is retained by the Agency and serves as the sole file copy of the approved application. The review copy is destroyed. If there is a requirement for a bioequivalence study, then the review copy is divided into two parts containing the scientific information needed for FDA review of the application by different scientific reviewers. One part should contain information about chemistry, manufacturing and controls, and one part should contain information about bioavailability and bioequivalence.

Each part contains sections (e.g., "Labeling") that permit concurrent review of the application by various review disciplines. (See Review Copy--Additional Guidance for further explanation.)

An applicant may submit all or portions of the archival copy of the application in any form that the applicant and FDA agree is acceptable. Submission of electronic versions of the application are welcome, but should be discussed with the Office of Generic Drugs prior to actual submission.

Each application should be submitted in color-coded jackets. Information about the volume size and identification, the jacket specifications (including color coding), the size and quality of paper for text, and mailing instructions are shown in Attachment B.

B. Cover Letter

Each submission (whether original, amendment, supplement, or annual report) should include a dated cover letter with a clear, brief introductory statement. The cover letter should be on the letterhead of the applicant or the applicant's agent. If letterhead other than that of the applicant is used, an explanation of why the applicant's letterhead was not used should be included. The cover letter should assist the reviewer by including, at a minimum, the following:

1. Purpose of the submission;

2. Type of submission (ANDA, AADA, amendment, supplement, annual report, or resubmission as a result of prior withdrawal of an application);

3. Name, title, signature, and address of the applicant;

4. Proprietary name (if any) and established name of the drug product;

5. Number of volumes submitted.

For amendments, supplements, and annual reports, either the cover letter or the narrative for the section that was changed by the new submission should contain a description of the specific changes to previously submitted material. A comparison between the new information and the old information is preferred.

The cover letter should include a clear heading for special situations, such as: "Major" or "Minor" Amendment, or "Special Supplement--Changes Being Effected," or "Supplement--Expedited Review Requested."

C. Table of Contents

Each original application or other submission, as applicable, should include a table of contents. The purpose of the table of contents is to tell the reviewer where information can be found in the application. Attachment C provides a suggested table of contents for a typical ANDA. Attachment C is intended to complement the applicable regulations and can be used for general guidance in assembling the application, but should not be relied on solely for determining contents of the submission. Although not all sections apply to AADAs, this table of contents may be adjusted to accommodate the specific needs of the AADA.

If a section of the suggested table of contents is not used, insert a page behind the tab for that section (see below) and state "not applicable" in the table of contents and in the text. If a new subsection (line item within a section currently on the table of contents) is added to the table of contents, modify the application accordingly. Additional sections should be placed at the end of the table of contents and begin with number XXII (see suggested table of contents).

If the archival or review copy of the application requires more than one volume, the table of contents should be duplicated and placed in each volume. Thus, the same table of contents should be used in all jacketed volumes. (See Review Copy--Additional Guidance for further explanation regarding the separation of the review copy.)

D. Tabs

The contents of the submission should be organized by sections, and each section should be identified by a tab that corresponds to the section set forth in the table of contents. The tab shows the number and brief descriptive name of the section it identifies (e.g., Attachment C, "Section VI--Bioavailability/Bioequivalence"). Applicants may also use tabs for subsections within a section. In this event, use of a different color tab for subsections is useful. However, too many tabs may result in an unwieldy application.

E. Pagination

All pages of the archival copy of the application (except the tab pages) should be numbered in sequence. The sequence begins with page number one for the front side of the Application Form (Section I of Attachment C) and increases consecutively to the last page of the application. The sections and line items in the table of contents should accurately reflect the page numbers of the corresponding text.

The page number should be placed on the bottom center of each sheet of paper. Each submission after the original application (e.g., amendments or supplements) should also begin with page one and run consecutively to the end of that submission.

Correct pagination is essential to the reviewer in locating material in an application. Correct, consistent pagination between the text and the table of contents is especially important when an application consists of more than one volume.

F. Review Copy -- Additional Guidance

In addition to the archival copy, the applicant should submit a review copy. The review copy may contain two parts if bioavailability/ bioequivalence data is required, one part containing primarily chemistry, manufacturing, and controls data and the other part containing bioavailability/bioequivalence data. (Note that there will be gaps in the page numbering of the review copy if a bioavailability/bioequivalence part is required, since neither part contains all sections in the archival copy. See Attachment A.)

Each part may contain one or more volumes, depending on the size of the submission.

Each volume of the review copy should contain the complete table of contents, identical to that of the archival copy.

For identification purposes, the chemistry, manufacturing, and controls review part should be contained in a red jacket (or jackets), while the bioavailability/bioequivalence

review part should be contained in an orange jacket (or jackets).

Sections contained in the review copy should be identical to those of the archival copy, including use of the same page numbers.

For the typical ANDA (see Attachment C), both parts will contain Sections I through V, and VII. The chemistry, manufacturing, and controls part will also contain Sections VIII through XXI, and the bioavailability/bioequivalence part would contain Section VI (see Attachment A).

G. Field Copy--Additional Guidance

In addition to the archival copy, domestic applicants must submit a certification (21 CFR 314.94) that a "true" third/field copy of the technical sections (Chemistry, Manufacturing and Controls) of the application has been submitted to the appropriate FDA District Office.

Foreign applicants should submit the field copy to the Office of Generic Drugs. (See Attachment B for mailing address and specifications.)

ATTACHMENT A

COMPOSITION OF REVIEW COPIES

The following table illustrates the suggested separation of text for the "red" part of the review copy containing chemistry, and for the "orange" part of the review copy containing bioavailability/bioequivalence. The "sections" referred to are those shown on the suggested table of contents in Attachment C.

TABLE: COMPOSITION OF REVIEW COPIES CORRESPONDING TO SUGGESTED TABLE OF CONTENTS (ATTACHMENT C)

SECTION	RED COPY	ORANGE COPY
I	X	X
II	X	X
III	X	X
IV	X	X
V	X	X
VI (BIO)	-	X
VII	X	X
VIII - XXI	X	-

ATTACHMENT B

SUGGESTED SPECIFICATIONS

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1. VOLUME SIZE AND IDENTIFICATION

A. Each volume of an application should not be more than 3 inches thick.

B. The name and address of the applicant, the name of the drug, dosage form, and strength of the drug should be displayed on the front of the jacket of each volume.

C. Please do NOT number the volumes. The Agency will number the volumes.

D. All original abbreviated applications should be submitted in jackets. Small amendments or supplements not contained within jackets should be bound with fasteners (NO STAPLES) rather than by three-ring binders.

2. JACKET COLOR AND ORDERING

A. The volume jackets of the application should be color coded.

	Color	Form Number
Archival Copy	Blue	FDA 2626

Review Copy: (See Review Copy--Additional Guidance for further information.)

(1) Chemistry, Manufacturing and Controls (not containing Bio)
Red FDA 2626a

(2) Bioavailability/Bioequivalence
Orange FDA 2626c

Field Copy: (See Field Copy--Additional Guidance for further information.)

Burgundy FDA 2626h

B. A limited number of jackets may be obtained free of charge by sending a Special Order form (obtained from CFPDC--see below) that states the form number (as shown above), quantity, name, address and telephone number of requestor to:

Consolidated Forms and Publications Distribution Center
Washington Commerce Center
3222 Hubbard Road
Landover, Maryland 20785

Additional jackets, with the following specifications, may be purchased from a commercial source:

(l) Archival Copy

Polyvinyl type jacket .023 to .025 gauge
Front cover: 9" x ll-l/2"
Back cover: 9" x 12" with a full l/2" tab along the top edge.
Color: as stated above
Hidden reinforced 1" hinges for front and back covers.
Rounded outside corners for front and back covers.

(2) Review Copy

Extra-heavy paper jacket
Front cover: 9" x ll-l/2"
Back cover: 9" x 12" with a full l/2" tab along the top edge.
Color: as stated above
Hidden reinforced 1" hinges for front and back covers.
Rounded outside corners for front and back covers.

(3) Field Copy

Extra-heavy paper jacket
Front cover: 9" x ll-l/2"
Back cover: 9" x 12" with a full l/2" tab along the top edge.
Color: as stated above
Hidden reinforced 1" hinges for front and back covers.
Rounded outside corners for front and back covers.

III. PAPER SIZE AND QUALITY

A. Good U. S. standard quality bond, 8-1/2" x 11", loose leaf paper.

B. Three-hole punched on left hand margin.

C. One-inch margins to accommodate readability after binding and photocopying.

D. Typing on both sides of paper is allowed if bleeding through the other side does not occur.

E. Paper should accommodate photocopying.

IV. MAILING

A. The packing carton should identify the contents by:

Drug name
Applicant's name
Applicant's address
"Archival Copy Enclosed" or "Review Copy Enclosed" (or both)

B. Mail abbreviated applications to:

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

C. Archival and review copies of abbreviated applications sent by overnight courier service or a parcel service should be sent to:

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTACHMENT C

SUGGESTED TABLE OF CONTENTS

This suggested Table of Contents applies to an original abbreviated new drug application (ANDA). Although not all sections apply to an abbreviated antibiotic application (AADA), this table of contents may be adjusted to accommodate the specific needs of the AADA.

The page numbers shown, 1-214, are for illustrative purposes, only.

Submitted [314.94(a)(11)]

3. Letters of Authorization (Two Copies) 214

This notice is issued under section 10(a)(1) and (a)(2) of the Federal Advisory Committee Act (5 U.S.C. app. 2), and FDA's regulations (21 CFR part 14) on advisory committees.

Dated: April 16, 1997.

Michael A. Friedman,

Deputy Commissioner for Operations.

[FR Doc. 97-10477 Filed 4-22-97; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of the Committee: Dental Drug Products Panel Plaque Subcommittee (Nonprescription Drugs) of the Medical Devices Advisory Committee, code 12518.

General Function of the Committee: The committee reviews and evaluates data on the safety and effectiveness of marketed and investigational devices and makes recommendations for their regulation. The Dental Products Panel of the Medical Devices Advisory Committee functions at times as a nonprescription drugs advisory panel. As such, the committee reviews and evaluates available data concerning the safety and effectiveness of active ingredients, and combinations thereof, of various currently marketed nonprescription drug products for human use, the adequacy of their labeling, and advises the Commissioner of Food and Drugs on the issuance of monographs establishing conditions under which these drugs are generally recognized as safe and effective and not misbranded.

Date and Time: The meeting will be held on May 8 and 9, 1997, 8:30 a.m. to 5 p.m. Open public hearing portions are scheduled from 8:30 a.m. to 12 m. on May 8, 1997, and from 8:30 a.m. to 12 m. on May 9, 1997.

Location: Ramada Inn—Bethesda, Ambassador Ballroom, 8400 Wisconsin Ave., Bethesda, MD.

Contact Person: Andrea G. Neal or LaNise S. Giles, Center for Drug Evaluation and Research (HFD-21), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-5455, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12518. Please call the Information Line for up-to-date information on this meeting.

Agenda: On May 8, 1997, the subcommittee will discuss the safety of the individual ingredients menthol, thymol, methyl salicylate, and eucalyptol, and continue its discussion of the effectiveness of these ingredients. The subcommittee will also discuss zinc citrate. In addition, there will be continued discussion and/or summaries and voting on the ingredients cetylpyridinium chloride, Microdent, sodium lauryl sulfate, and C31G-Therasol® .

On May 9, 1997, the subcommittee will discuss the safety and effectiveness of the combination of hydrogen peroxide and povidone iodine, and the effectiveness of the combination of hydrogen peroxide, sodium citrate, zinc chloride, and sodium lauryl sulfate. There will also be continued discussion and/or summaries and voting on the ingredients xylitol, sodium bicarbonate, and the combination of hydrogen peroxide and sodium bicarbonate. In addition, the subcommittee will discuss general recommendations for antiplaque combination ingredients.

Procedure: The meeting is open to the public. Interested persons may present data, information, or views, orally, or in writing, on issues pending before the committee. Written submissions may be made to the contact person by April 30, 1997. Those desiring to make formal presentations should notify the contact person before April 30, 1997, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

FDA regrets that it was unable to publish this notice 15 days prior to the May 8 and 9, 1997, Dental Drug Products Panel Plaque Subcommittee (Nonprescription Drugs) of the Medical Devices Advisory Committee meeting. Because the agency believes there is some urgency to bring this issue to public discussion and qualified members of the Dental Drug Products Panel Plaque Subcommittee (Nonprescription Drugs) of the Medical Devices Advisory Committee were available at this time, the Commissioner concluded that it was in the public interest to hold this meeting even if there was not sufficient time for the customary 15-day public notice.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: April 17, 1997.

Michael A. Friedman,

Deputy Commissioner for Operations.

[FR Doc. 97-10479 Filed 4-22-97; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97D-0164]

Positron Emission Tomography Drug Products; Draft Guidance for Industry on Content and Format of an Abbreviated New Drug Application; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance document entitled "Guidance for Industry: Content and Format of an Abbreviated New Drug Application (ANDA)—Positron Emission Tomography (PET) Drug Products." This draft guidance is intended to assist applicants who wish to submit an ANDA for Fludeoxyglucose F18 Injection. The draft guidance is one of several topics to be discussed at an April 28, 1997, FDA workshop on PET radiopharmaceutical drug products. The agency is requesting comments on this draft guidance.

DATES: Written comments may be submitted on the draft guidance document by June 28, 1997. General comments on agency guidance documents are welcomed at any time.

ADDRESSES: Submit written requests for single copies of the draft guidance document to the Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send two self-addressed adhesive labels to assist that office in processing your request. Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. Requests and comments should be identified with the docket number found in brackets in the heading of this document. A copy of the draft guidance document and received comments will be available for public examination in the Dockets

Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Peter Rickman, Center for Drug Evaluation and Research (HFD-615), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-0315.

SUPPLEMENTARY INFORMATION: FDA is announcing the availability of a draft guidance document entitled "Guidance for Industry: Content and Format of an Abbreviated New Drug Application (ANDA)—Positron Emission Tomography (PET) Drug Products." PET is a medical imaging modality used to assess the body's biochemical processes. Radionuclides are manufactured into PET radiopharmaceutical drug products that are administered to patients for medical imaging. The images of the body's biochemical processes are then evaluated, generally for diagnostic purposes.

Under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)), ANDA's may be submitted for drug products that are the same as a listed drug, i.e., identical in active ingredient(s), dosage form, strength, route of administration and conditions of use, except for those uses for which approval cannot be granted because of exclusivity, or for which an existing patent may be omitted (21 CFR 314.92). Because a new drug application (NDA) for Fludeoxyglucose F18 Injection (NDA 20-306) was approved on August 19, 1994, for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures, ANDA's may be submitted for drug products that are the same as this reference listed drug product and for the same use. The purpose of the draft guidance document is to assist applicants who wish to submit an ANDA for Fludeoxyglucose F18 Injection. The draft guidance is one of several issues to be discussed at an April 28, 1997, FDA workshop on PET radiopharmaceutical drug products. The workshop, which will be held in Rockville, MD, was announced in the Federal Register on March 14, 1997 (62 FR 12218). Other issues to be discussed at the workshop include: Registration and listing requirements, chemistry and manufacturing controls, sterility assurance, bioequivalence requirements, and labeling.

This guidance document represents the agency's current thinking on the content and format of an ANDA for PET radiopharmaceutical drug products. It does not create or confer any rights for, or on, any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

Interested persons may submit written comments on the draft guidance document to the Dockets Management Branch (address above). 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 draft guidance document and received comments also may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

An electronic version of this draft guidance is available on the Internet using the World Wide Web (http://www.fda.gov/cder/guidance.htm).

Dated: April 18, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97-10542 Filed 4-22-97; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

Availability of Funds for Planning Grants To Establish Comprehensive HIV Primary Health Care Services; The Ryan White Comprehensive AIDS Resources Emergency Act of 1990, as Amended by the Ryan White CARE Act Amendments of 1996

AGENCY: Health Resources and Services Administration, HHS.

ACTION: Availability of Grants to Support Planning Activities To Establish Comprehensive Primary Health Care Services with Respect to Human Immunodeficiency Virus (HIV) Disease.

SUMMARY: The Health Resources and Services Administration (HRSA) announces that applications will be accepted for fiscal year (FY) 1997 discretionary grants to support communities and health care service entities in their preparations to provide a high quality and broad, comprehensive scope of primary health care services for people in underserved areas who are living with HIV or at risk of infection. The Ryan White Title III HIV Planning Grants are intended to assist health care service entities to qualify for grant support under the Ryan White Title III Early Intervention Services Program.

These grants are awarded under the provisions of Part C of Title XXVI of the Public Health Service (PHS) Act, as amended by the Ryan White CARE Act Amendments of 1996, Public Law 104-146 (42 U.S.C. 300ff-51—300ff-67).

The PHS is committed to achieving the health promotion and disease prevention objectives of Healthy People 2000, a PHS-led national activity for setting health priorities. This grant program is related to the objectives cited for special populations, particularly people with low income, minorities, and the disabled, which constitute a significant portion of the homeless population. Potential applicants may obtain a copy of *Healthy People 2000* (Full Report; Stock No. 017-001-00474-0) or *Healthy People 2000* (Summary Report; Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, D.C. 20402-9325 (telephone 202-783-3238).

PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children.

DUE DATE: Applications are due on May 23, 1997. Applications will be considered to have met the deadline if they are: (1) received on or before the deadline date; or (2) postmarked on or before the established deadline date and received in time for orderly processing. Applicants should request a legibly dated U.S. Postal Service postmark or obtain a legibly dated receipt from a commercial carrier or U.S. Postal Service. Private metered postmarks are not acceptable as proof of timely mailing. Applications postmarked after the announced closing date will not be considered for funding.

ADDRESSES: Application kits (Form PHS 5161-1) with revised face sheet DHHS Form 424, as approved by the Office of Management and Budget under control number 0937-0189 may be obtained from, and completed applications should be mailed to HRSA Grants Application Center, 40 West Gude Drive, Suite 100, Rockville, MD 20850 (telephone: 1-888-300-4772). The Bureau of Primary Health Care's Office of Grants Management can also provide assistance on business management issues, and can be reached at 4350 East-

Guidance for Industry

Content and Format of an Abbreviated New Drug Application (ANDA) — Positron Emission Tomography (PET) Drug Products

With specific information for ANDAs for Fludeoxyglucose F18 Injection

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Draft release for comment on: April 18, 1997.

Comments and suggestions regarding this draft document should be submitted by June 28, 1997, to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm 1-23, Rockville, MD 20857. All comments should be identified with the docket number 97D-0164. For questions regarding this draft document, contact Peter Rickman, at (301) 594-0315.

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 1997

Draft — Not for implementation

Table of Contents

Draft — Not for implementation

GUIDANCE FOR INDUSTRY[1]

CONTENT AND FORMAT OF AN ABBREVIATED NEW DRUG APPLICATION (ANDA) — POSITRON EMISSION TOMOGRAPHY (PET) DRUG PRODUCTS

With specific information for ANDAs for Fludeoxyglucose F18 Injection

I. INTRODUCTION

Under 21 U.S.C. 355(j), Abbreviated New Drug Applications (ANDAs) may be submitted for drug products that are the same as a listed drug. FDA's implementing regulations at 21 CFR 314.92 state that the term *same as* means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except for those uses for which approval cannot be granted because of exclusivity, or for which an existing patent may be omitted. Because a New Drug Application (NDA) for Fludeoxyglucose F18 Injection was submitted by Downstate Clinical PET Center and was approved on August 19, 1994, (NDA 20-306), ANDAs may be submitted for drug products that are the same as this reference listed drug (RLD) product.

This guidance is provided to assist applicants who wish to submit an ANDA for Fludeoxyglucose F18 Injection. The Center for Drug Evaluation and Research's *Guidance for Industry: Organization of an Abbreviated New Drug Application (ANDA) and an Abbreviated Antibiotic Application (AADA)*, provides information regarding the organization of an ANDA.

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[1]This draft guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This draft guidance represents the Agency's current thinking on the content and format of an ANDA for PET radiopharmaceutical drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, CDER, FDA, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573, (Internet) http://www.fda.gov.cder/guidance.htm.

II. GENERAL INFORMATION

The content and format of abbreviated applications is described in 21 CFR 314.94. This regulation also requires the submission of three copies of the application: an archival copy, a review copy, and a field copy.[2]

An applicant should submit a complete archival (original) and review (duplicate) copy of the application that includes the following information:

A. Cover Letter

The application should include a signed and dated cover letter which includes a clear, brief introductory statement. The cover letter should be on the letterhead stationery of the applicant. The cover letter should contain the following information:

1. Purpose of the submission;

2. Type of submission (ANDA, AADA, amendment, supplement, annual report, or resubmission as a result of prior withdrawal of an application);

3. Name, title, signature, and address of the applicant;

4. Proprietary name (if any) and established name of the drug product;

5. Number of volumes submitted.

B. Letters of Authorization

1. Agent

Domestic Applicants - If a domestic firm uses an agent, a letter of authorization allowing the agent to act on behalf of the applicant should be included in the application following the cover letter.

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[2] On March 20, 1997, FDA published a final rule (62 FR 13429) that would allow FDA to accept, under certain circumstances, electronic records and electronic signatures as equivalent to paper records and handwritten signatures executed to paper. This rule takes effect on August 20, 1997. For information on how to prepare an electronic ANDA contact the Office of Generic Drugs.

2. Drug Master File (DMF)

DMF letters of authorization grant the Agency the authority to refer to information in a DMF during the review of an ANDA (21 CFR 314.420). The letter of authorization should be on the DMF holder's letterhead, and dated and signed with an original signature. The letter should cite the DMF holder's name, drug name, and DMF number. If the referral is made by a third party (i.e., another corporate entity, agent, or supplier), a letter from the DMF holder should be provided giving the third party the authorization to grant referrals to the DMF. If the applicant intends to rely on DMF information concerning the bulk drug substance, authorization should be granted by the holder of the DMF for each source of bulk drug substance. This letter should be placed in the chemistry, manufacturing, and controls section along with the information submitted for the active ingredient. (See also letters dated Nov. 8, 1991, and April 8, 1994.)

If the applicant is also the manufacturer of the active ingredient, Fludeoxyglucose F18 applicants would not have to provide a DMF reference for the bulk drug substance.

C. Debarment Certification/List of Convictions

Use of a debarred individual/firm, within the meaning of 306(a) and (b) of the Federal Food, Drug and Cosmetic Act (the act) [21 U.S.C. 335a(a) and (b)], may preclude the approval of the application.

The 1992 Generic Drug Enforcement Act authorizes the FDA to debar an individual, convicted of certain crimes or found to have engaged in certain types of conduct, from providing any services to a drug product applicant. The law also authorizes the FDA to debar a firm convicted of certain crimes from obtaining or participating in certain subsequent drug approvals.

Under section 306(k)(2) of the act [21 U.S.C. 335a(k)(1)], any application for approval of a drug product submitted after June 1, 1992, must include a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)] in connection with such application. In addition to the certification requirement, section 306(k)(2) of the act [21 U.S.C. 335a(k)(2)] requires that all ANDAs and AADAs contain a conviction information statement listing any convictions the firm or its affiliated persons may have that could lead to debarment. The applicant should provide a list of any relevant convictions, the name of the person/firm convicted, the title of the section of the federal or state statute

involved, the sentencing date, the court entering judgment, and the case number, if known, and a brief description of the offense. In addition, the applicant should explain the role of each convicted person in the development of the application. The debarment certification and conviction information, which usually follows the cover letter, should be signed by a responsible officer of the applicant or by the individual responsible for signing the application. (See also letters dated July 27, 1992, Jan. 15, 1993, and April 8, 1994.)

Examples of a debarment certification and a conviction information statement follow:

Debarment Certification:

(Name of applicant) certifies that (the applicant) did not and will not use in any capacity the services of any person debarred under section 306 of the act in connection with this application.

If convictions exist for the applicant or an affiliated person responsible for the development or submission of the application that could lead to a debarment, use the following convictions statement.

Convictions Statement:

(Applicant) lists the following convictions for (applicant and/or affiliated persons):

These convictions are described in section 306(a) and (b) of the act [21 U.S.C. 335a(a) and (b)]. The list must contain all such convictions that occurred within 5 years before the date of the application (306(k)(2)).

If neither the firm nor any of its affiliated persons has convictions to list, a statement should be submitted to the effect that neither the applicant nor its affiliated persons responsible for the development or submission of the application has been convicted of a relevant offence within the last five years.

D. Field Copy Certification

The applicant must submit a certification that indicates that an accurate third copy of the technical sections (chemistry, manufacturing, and controls) of the application has been submitted to the appropriate FDA district office (see 21 CFR 314.94(d)(5) and 314.440(a)(4)). This certification should contain an original signature.

If questions arise on issues involving the submission of the third copy, please contact the Office of Compliance in the Center for Drug Evaluation and Research at (301) 594-0054.

Example of a field copy certification follows:

(Name of applicant) certifies that the field copy is a true copy of the technical section of the application described in 21 CFR 314.94(d)(5).

III. CONTENT AND FORMAT OF AN ABBREVIATED APPLICATION

A. Application Form

Form FDA 356h should be completed, signed with an original signature, and contain the information required under 21 CFR 314.94(a)(1). The form should also list all pertinent DMFs. The applicant should identify the RLD (reference listed drug) on Form FDA 356h.

Under 21 CFR 314.50(a)(3), the applicant must submit a statement as to whether the applicant proposes to market the drug product as a prescription or over-the-counter product. If the correct box is checked on Form FDA 356h regarding prescription or over-the-counter status, no additional statement is necessary.

Each application should include a table of contents [21 CFR 314.94(a)(2)] following Form FDA 356h. For a suggested table of contents, refer to the *Guidance for Industry: Organization of an Abbreviated New Drug Application (ANDA) and an Abbreviated Antibiotic Application (AADA).*

The table of contents helps the reviewer locate information in the application. Each section of the application should be delineated by dividers and tabbed, and the pages should be numbered sequentially.

B. Basis for Abbreviated New Drug Application Submission

The applicant must cite the name of the RLD including its dosage form and strength (21 CFR 314.94(a)(3)(i)), as identified in the publication, *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book), by the symbol "+". The product designated with the symbol "+" is the drug product selected by the Agency as the reference standard for conducting bioequivalence testing.

NDA 20-306, Fludeoxyglucose F 18 Injection USP, held by Downstate Clinical PET Center is the applicable RLD.

The ANDA product must have the same active ingredient, dosage form, strength, and route of administration as the reference listed drug product [21 CFR 314.94(a)(5)(i)(A) and 314.94(a)(6)(i)(A)]. A change from the RLD in one or more of these items requires the submission of a suitability petition to obtain permission to submit an ANDA with such change [21 CFR 314.93]. The strength of the drug product refers to the concentration or amount of active ingredient in the drug product. Generally, a change in either the concentration or total volume of a parenteral drug product will constitute a change in strength for which a suitability petition is required under 21 CFR 314.93(c).

C. Patent Certification and Exclusivity Statement

1. Patent Certification

Except as provided in 21 CFR 314.94(a)(12)(iv), the applicant must provide a certification with respect to each patent issued by the United States Patent and Trademark Office that in the opinion of the applicant and to the best of its knowledge claims the RLD or claims a use of such listed drug for which the applicant is seeking approval under section 505(j) of the act [21 U.S.C. 355(j)] and for which information is required to be filed under section 505(b) of the Act (21 U.S.C. 355(b)) and 21 CFR 314.53. As stated under this section of the Act and 21 CFR 314.94(a)(12), the applicant must provide for each patent the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

- That the patent information has not been submitted to the FDA. The applicant shall title such a certification "Paragraph I Certification."
- That the patent has expired. The applicant shall title such a certification "Paragraph II Certification."
- The date on which the patent will expire. (e.g. Patent No. _____will expire on _____.) The applicant shall title such a certification "Paragraph III Certification."
- Or, that the patent is invalid, unenforceable, or will not be infringed by the manufacture, use or sale of the drug product for which the abbreviated application is submitted. (This type of certification indicates that the applicant is challenging the patent). The applicant shall

title such a certification "Paragraph IV Certification."

A Paragraph IV certification must be accompanied by a statement that the applicant will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with the requirements under 21 CFR 314.95 with respect to the content of the notice.

Under 21 CFR 314.94(a)(12)(i)(A)(1), applications for Fludeoxyglucose F 18 Injection must contain a Paragraph I certification if patent information has not been submitted to the Agency.

Example of a Paragraph I patent certification follows:

In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the listed drug referred to in this application or that claim a use of the listed drug, 21 CFR 314.94(a)(12)(ii).

A list containing patent information may be located in the Patent and Exclusivity Addendum in the Orange Book and its supplements. Patent information should be verified with the latest Orange Book edition and/or supplement.

2. Exclusivity Statement

Exclusivity is granted by the Agency for certain drug products (21 CFR 314.108). A list containing exclusivity information can be located in the Patent and Exclusivity Addendum in the Orange Book and its supplements. (See also letters dated Oct. 31, 1986, April 28, 1988, and July 29, 1988.)

A statement addressing exclusivity must be submitted even if no exclusivity exists [314.94(a)(3)(ii)].

Example where no exclusivity exists (pertaining to Fludeoxyglucose F18 Injection): According to the publication, Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) *the reference listed drug is not entitled to a period of marketing exclusivity under Section 505(j)(4)(D) of the act [21 U.S.C. 355(j)(4)(D)].*

Exclusivity information should be verified with the latest *Orange Book* edition and/or supplement.

D. Comparison Between Generic Drug and Reference Listed Drug

1. Conditions of Use

Under CFR 314.94(a)(4), the applicant must submit a statement that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the drug product have been previously approved for the RLD. The applicant is required to reference the annotated proposed labeling and the currently approved labeling for the RLD [21 CFR 314.94(a)(4)].

2. Active Ingredients

The applicant must provide a statement that the active ingredient in the proposed drug product is the same as the active ingredient in the RLD (21 CFR 314.94(a)(5)(A)). The applicant must also reference the annotated proposed labeling and the currently approved labeling for the RLD (21 CFR 314.94(a)(5)(B)).

3. Route of Administration, Dosage Form, and Strength

Under 21 CFR 314.94(a)(6), the applicant must provide a statement that the route of administration, dosage form, and strength of the proposed drug product are the same as those of the RLD except for any differences that have been the subject of an approved ANDA suitability petition. The applicant should reference the annotated proposed labeling and the currently approved labeling for the RLD. If differences exist due to the approval of an ANDA suitability petition, these differences should be delineated and a copy of the approval letter for the petition should be included.

Example format follows:

The conditions of use prescribed, recommended, or suggested in the labeling proposed for the generic drug have been previously approved for the reference listed drug. [Please refer to the labeling section for a comparison of (applicant's) annotated proposed labeling and to the currently approved labeling for the reference listed drug.] The active ingredient, route of administration, dosage form, and strength are the same as the reference listed drug.

A detailed comparison of the proposed drug and the reference listed drug follows:

	Generic Drug Product	*Downstate Clinical PET Center*
Conditions of use:	*FDG injection is indicated in PET for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.*	*FDG injection is indicated in PET for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.*
Active ingredient:	*Fludeoxyglucose F 18*	*Fludeoxyglucose F 18*
Route of administration:	*Parenteral*	*Parenteral*
Dosage form:	*Solution*	*Solution*
Strength:	*6.8 - 35.7 mCi/mL*	*6.8 - 35.7 mCi/mL*

Under 21 CFR 314.93, a change from the RLD in strength, dosage form, or route of administration requires the submission of a suitability petition to obtain permission to file an ANDA with such a change. According to the Orange Book, the strength of the RLD for Fludeoxyglucose F18 ([^{18}F]FDG) Injection is 6.8 - 35.7 mCi/mL. The labeling of the drug product states that it contains 296 ± ~~3 mL of isotonic saline~~. Any change that affects the amount of the active ingredient or the concentration of the drug product (in mCi/mL) will be deemed to be a change in strength that, under 21 CFR 314.93, requires a suitability petition prior to filing the ANDA. Therefore, the use of a higher energy cyclotron may result in a more concentrated drug product for which a suitability petition is required under 21 CFR 314.93. In addition, a change in the total volume, and/or the amount of active ingredient, may result in a change of strength for which 21 CFR 314.93 requires a suitability petition.

168 mCi in 16 ± 3 mL of isotonic saline.

E. Labeling

Refer to the *Fludeoxyglucose F18 Injection Labeling Guidance* and the Aug. 4, 1993, letter.

A side-by-side comparison of the container labels and package insert with all differences annotated and explained for the RLD and the proposed drug product must be submitted in addition to the four copies of draft (or 12 copies of final printed) labeling (21 CFR 314.94(a)(8)).

F. Bioavailability and Bioequivalence

The applicant is required to provide information that shows that the drug product is bioequivalent to the RLD product upon which the applicant relies (21 CFR 314.94(a)(7)). (See also 21 CFR 314.94(a)(9)(ii) and (iii) and 21 CFR 320.22(b)(1).)

Any qualitative or quantitative differences in formulation from the RLD for parenteral drug products should be characterized and explained. A side-by-side comparison of the formulation of the proposed product and the RLD should be submitted. Analytical information and a physicochemical comparison should be included. Parenteral drug products may only differ in preservative, buffer, or anti-oxidant. If other changes are made in a parenteral drug product, an in vivo bioequivalence study may be needed.

Inactive ingredients used in the proposed generic drug product should have been previously approved in another drug product given by the same route of administration. The use of an approved inactive ingredient can be verified in the *Inactive Ingredient Guide*. The quantities of the inactive ingredient should not exceed the *Inactive Ingredient Guide* range. (Also refer to the *Interim Inactive Ingredients Policy* for information regarding exception and nonexception excipients.)

A waiver of evidence of in vivo bioequivalence may be requested for Fludeoxyglucose F 18 Injection. For certain drug products, such as Fludeoxyglucose F18 injection (abbreviated as [^{18}F]FDG), the in vivo bioequivalence may be self-evident. The FDA will waive the requirement for the submission of evidence obtained in vivo demonstrating bioequivalence if FDA determines that in vivo bioequivalence is self-evident. For example, in vivo bioequivalence may be self-evident if the drug product meets the following criteria:

- The drug product is a parenteral solution intended solely for administration by injection.

- The drug product contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application [21 CFR 320.22(b)].

Example of request for waiver of evidence of in vivo bioequivalence:

The (applicant) requests that the FDA waive the requirement for the submission of evidence demonstrating in vivo bioequivalence for (the proposed drug product). The (drug product) meets the provisions of 21 CFR 320.22(b)(1)(i) and (ii).

In addition, under 21 CFR 320.22(e), for good cause, FDA may waive a requirement for submission of evidence of in vivo bioavailability if FDA determines that a waiver is compatible with the protection of the public health.

G. Components and Composition

Components (active and inactive ingredients) and composition of the drug product should be included. For Fludeoxyglucose F18 Injection, the active ingredient (drug substance) is Fludeoxyglucose F 18 (2-deoxy-2-[^{18}F]fluoro-D-glucose).

All inactive ingredients should be identified by their chemical names and their quantity and/or concentration (e.g., mg/mL) should be included. Applicants should refer to 21 CFR 314.94(a)(9)(iii) concerning the inactive ingredient changes permitted in a generic drug product intended for parenteral use. If inactive ingredients in the proposed product differ qualitatively and/or quantitatively from the RLD, information should be provided to demonstrate that the difference does not affect the safety of the proposed drug product. The submitted information should include, but need not be limited to, the following: (1) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients, and are within the same concentration range, (2) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (3) a comparison of the physical and chemical properties (e.g., pH, osmolarity, toxicity) of the proposed drug product with that of the RLD, and (4) information to show that the inactive ingredients do not affect these properties.

For [^{18}F]FDG, the Agency recognizes that the drug product formulated at the end of the synthesis (i.e., a batch) may be used as a single dose or as multiple doses. The quantitative composition of the unit dose may be assumed to be the same as that of the entire batch.

H. Raw Materials Controls

Information concerning the raw materials used for the manufacture of [^{18}F]FDG may be provided in the following format:

1. Components

    a. Name and Full Address(es) of the Supplier.

b. Method of Purification

If a component (e.g., mannose triflate, kryptofix) as received from its supplier is further purified or recrystallized, full information on this process, including the rationale, the method(s), and the solvents employed (if any) should be included in the application.

c. Specifications and Analytical Test Methods

For each component and inactive ingredient, the following information should be included:

i. The applicant should provide specifications and a test method for the identity of all components. The identity test should be performed prior to release of each lot of the material. Details of the analytical test method should be included in the application.

ii. If the suppliers of the raw materials are different than those listed in the RLD, then the suppliers should be validated. All raw material components should have acceptance specifications and be accepted with a certificate of analysis (COA). Full testing to determine the accuracy of the COA should be preformed. The supplier of the raw materials should be in compliance with Current Good Manufacturing Practice (CGMP) regulations. Once a supplier is validated, and a manufacturer wants to change suppliers, then the application should include data which demonstrates that the [^{18}F]FDG produced from raw materials from a new supplier are equivalent to the current supplier in terms of conformance with established specifications.

d. Retest Schedule

Each raw material should be retested periodically to determine that it still meets specifications. The periodic retest schedule should be provided.

2. Inactive Ingredients

For each inactive ingredient used in the drug product formulation, a statement of its quality [e.g., American Chemical Society (ACS), United States

Pharmacopeia (USP), National Formulary (NF)] should be provided. A certificate of analysis from a validated supplier that includes specifications and test results may be used to accept this material.

3. All Other Components (e.g. reagents, solvents)

A list of all other components which are used in the synthesis and purification of the drug product (e.g., all reactants, chemicals, solvents, reagents, that were not included above) should be included. A statement of the quality [e.g., American Chemical Society (ACS), United States Pharmacopeia (USP), National Formulary (NF)] of each component should be provided. A certificate of analysis, from a validated supplier, that includes specifications and test results may be used to accept this material.

4. Reference Standard

For [^{18}F] FDG, 2-deoxy-2-fluoro-D-glucose, a nonradioactive reference standard is used to establish and/or to verify the identity of Fludeoxyglucose F18 in the drug product. It also may be used for the determination of specific activity. The following information should be provided:

a. Source

Name and address of the supplier. If the reference standard is synthesized in-house, a statement to this effect should be included.

b. Proof of Identity

If the reference standard is purchased commercially, the applicant should include the certificate of analysis from its supplier. If the material is synthesized in-house, representative data to establish unequivocally the identity of the reference material lot as 2-deoxy-2-fluoro-D-glucose should be provided. The documentation should include complete spectrophotometric data, other applicable analytical data, as well as information on the synthetic route used.

I. Description of Manufacturing Facility

The following information should be provided (see also 21 CFR parts 210 and 211):

1. Name and full address(es) of the facility(ies) [including building and

room numbers] used in manufacturing, packaging, release testing, and stability testing of the drug product. Please include the Registration Number of the facility.

2. Certification that the facility is in compliance with the Current Good Manufacturing Practices (CGMPs) (see also letter of Oct. 14, 1994, on field/headquarters agreement). The applicant and any contract facilities should provide the following statement with an original signature.

(Name of Applicant) certifies that the methods used in and the facilities and controls used for the manufacturing, processing, packaging, testing, and holding of (product) conform, and will continue to conform, to the Current Good Manufacturing Practice regulations under 21 CFR parts 210 and 211.

J. Outside Firms Including Contract Testing Laboratories

The following information should be provided:

1. Name and full address of each facility. Please include the Registration Number.

2. The function(s) of each facility.

3. A certification that the facility is in compliance with the CGMPs.

K. Manufacturing and Processing Instructions

1. Manufacture of Drug Substance

The following information should be submitted:

a. Batch Formula

The batch formula for the test batch(es) (e.g., the batch used in support of the application) and the proposed production batches should be included. A complete list of all the ingredients (whether or not they remain in the finished product) and their amounts used in the batch formulation should be provided.

b. Production of the Radionuclide

i. Description of the Particle Accelerator

A brief description of the particle accelerator including its make and model should be provided. Applicants should note that the validation information on the accelerator demonstrating that the equipment is capable of consistently operating within the established limits and tolerances should be available on site for inspection.

ii. Operating Parameters

Operating parameters for the production at the manufacturing site should be defined. Examples of the operating parameters that should be included are maximum particle energy, beam current, and irradiation (bombardment) times. The value(s) or range of values for each defined operating parameter should be included in the application.

iii. Target Body

Specifications for the target body and the foil(s) which come in contact with the target material should be provided. These should include the composition of the target body and foil materials and the volume of the target. Information should be provided on procedures which are used to establish equivalency when an existing target body and/or foil(s) are replaced.

iv. Recycling of Oxygen-18 Enriched Water

If oxygen-18 [^{18}O]water is not recycled, this fact should be so stated. If it is recycled, procedures used for its reprocessing should be described. Information should be provided to demonstrate that the recycling and/or reprocessing of [^{18}O]water does not change the drug product quality impurity profile.

c. Synthesis and Purification of Drug Substance

i. Description of Radiochemical Synthesis and Purification Equipment

The equipment used for the synthesis and purification of

Fludeoxyglucose F18 should be described. It should include a schematic flow diagram of the equipment from the target to the vial filling unit. A description of various components (e.g., tubing, reaction vessel, columns, and the function of each purification component (e.g., various columns) should be included. The components that are replaced after each manufacturing operation, and the components that are replaced periodically should be identified. Suppliers for each of the replaceable components (e.g., various purification columns and filter) should be provided. The procedures used in the assembly of components should be described.

ii. Description of Radiochemical Synthesis and Purification Operation

Identify the components and the processes that are under computer control and the ones that are under manual control. Applicants should note that the validation information demonstrating that the equipment is capable of consistently operating within the established limits and tolerances should be available on site for inspection.

A stepwise description of the radiochemical synthesis and purification operation, including in-process controls (refer to section L.), should be provided. An acceptable range of yields of the radioactivity for the drug product should also be provided. The proposed range of yields should be justified.

iii. Post Synthesis Operations

A description of how the synthesis and purification equipment is prepared for a subsequent batch should be provided. All cleaning and purging procedures should be fully described.

2. Manufacture of Drug Product

a. Production Operations

The procedures used in the manufacture of the drug product should be described.

b. Reprocessing of the Drug Product

A drug product batch should not be reprocessed unless the reprocessing procedures and conditions have been approved in the ANDA. If an applicant intends to reprocess a drug product batch, the conditions (circumstances) and full reprocessing procedures should be submitted.

c. Proposed Master Production Records [21 CFR 314.94(a)(9)(i)]:

A copy of the blank master production record, including a description of the equipment, to be used for the manufacture of a lot of the drug product should be included.

3. Microbiological Validation

a. Introduction

i. Purpose

The recommendations in this document apply to ANDAs for sterile [^{18}F]FDG. These recommendations also apply to approved applications when supplements associated with sterile processing are submitted.

ii. Documenting Sterilization Process Validation

Sterilization process validation data should be generated using procedures and conditions that are fully representative and descriptive of the procedures and conditions proposed for manufacture of the product in the application.

The Center recognizes that for most [^{18}F]FDG products, the final drug product will be manufactured using aseptic techniques rather than terminal sterilization. The Center also recognizes that conventional methods for the validation of aseptic processes may not apply to the validation of the sterile production of [^{18}F]FDG due to the very small number of product units manufactured from a batch or lot, and its short half-life.

Technical subsections of an application are often reviewed apart from the main body of the application. For this reason, it is

recommended that the microbiology subsection include an introductory description of the drug product (syringe, vial, glass, plastic, closure system) and the product's intended use. It is further recommended that the information describing sterilization processes be filed in a subsection (or volume) of the chemistry manufacturing, and controls (CMC) portion of an application. This permits the CMC subsections to be reviewed simultaneously by different reviewers in different locations.

b. Information for Terminal Moist Heat Sterilization Processes

It is not expected that FDG-F18 products will be sterilized by terminal moist heat processes. Information relating to aseptic processing for the manufacture of FDG-F18 drug products is provided under "Information for Aseptic Fill Manufacturing Processes" (section c.). However, should FDG-F18 be sterilized by terminal moist heat methods, information should be submitted in support of sterility assurance as described in Section II of the *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.

c. Information for Aseptic Fill Manufacturing Processes

The following types of information should be submitted in support of sterility assurance for FDG-F18 manufactured by aseptic processing. The finished drug product should be described including the product solution (i.e., composition and pH) and the container-closure system(s) to be sterilized including size(s), fill volume, or secondary packaging. The route of product administration and the range of product dosage should be provided.

i. Buildings and Facilities

A brief description of the manufacturing building and aseptic facilities should be provided. The following information should be included.

- Floor Plan - A floor plan of the area(s) housing the aseptic filling facilities including preparation areas should be provided. The air cleanliness class of each area should be identified (e.g., Class 100, Class 10,000, Class 100,000).

Isolators or barrier systems should be identified.

- Location of equipment - The placement of all critical equipment including, but not limited to, laminar flow hoods, autoclaves, and filling devices should be identified. Equipment within barrier or isolation systems should be noted.

ii. Overall Manufacturing Operation

The overall manufacturing operation including, for example, solution compounding, component preparation, filling, capping, and aseptic assembly should be described. The normal flow (movement) of product and components from formulation to finished dosage form should be identified and indicated on (or in relation to) the floor plan described above. The following information should be considered when describing the overall manufacturing operation.

- Drug Product Solution Filtration - The specific bulk drug product solution filtration processes, including the use of tandem filter units, prefilters, and bacterial retentive filters should be described. A summary should be provided containing information and data concerning the validation of the retention of microbes and compatibility of the filter used for the specific product. For simple aqueous solutions, a certification from the filter manufacturer is often adequate. Effects of the filter on the product formulation should be described (e.g., adsorption of preservatives or active drug substance, or extractables).

- Specifications Concerning Holding Periods - 21 CFR 211.111 requires the establishment of appropriate time limits for completing each phase of production to ensure the quality of the drug product. Therefore, specifications concerning any holding periods between the compounding of the bulk drug product and its filling into final containers should be provided. These specifications should include, for example, times, temperatures, conditions of storage. Procedures used to protect microbiological quality of the bulk drug or components

during these holding periods should be indicated. Maintenance of the microbiological quality during holding periods may need verification. These technical burdens may be reduced if components of the drug solution are prepared fresh each day and maintained sterile prior to compounding.

- Critical Operations - The critical operations that expose product or product contact surfaces to the environment (such as transfer of sterilized containers or closures to the aseptic filling areas) should be described. Any barrier or isolation systems should be described.

iii. Sterilization and Depyrogenation of Containers, Closures, Equipment, and Components

The sterilization and depyrogenation processes used for containers, closures, equipment, components, and barrier systems should be described. A description of the methods for validation of these processes should be provided including, where applicable, heat distribution, and penetration summaries, biological challenge studies (microbiological indicators and endotoxin), and routine monitoring procedures. Data (including controls) demonstrating distribution and penetration of the sterilant and microbiological efficacy of each process should be submitted. For applicants using drug product containers which are purchased sterile from a vendor, a certificate from the vendor may be provided to substitute for the above information.

- Bulk Drug Solution Components That are Sterilized Separately - If the bulk drug solution is aseptically formulated from components that are sterilized separately, information and data concerning the validation of each of these separate sterilization processes should be provided.

- Sterilization Information in the Batch Records - The batch record supplied with the chemistry, manufacturing, and controls section of the application should identify the validated process(es) to be used for sterilization or depyrogenation of any container-closure components. This information may be included in the batch record by

reference to the validation protocol or standard operating procedure (SOP), or by reference to the vendor certificate for drug product containers purchased sterile from a vendor.

iv. Procedures and Specifications for Media Fills

Media fills are simulated manufacturing operations using microbiological growth medium in place of drug product. The procedures and specifications used for media fills, and summaries of results for validation using the same container-closure system and filling process that is to be used for the product should be described. The microbiological testing method(s) used should be described. Any procedural deviations between the media fill and the production process should be indicated. A summary of recent media fill results (usually for at least 3 successful trials), including failures, should be provided.

v. Actions Concerning Product When Media Fills Fail

Descriptions of investigation plans and appropriate corrective actions should be provided.

vi. Microbiological Monitoring of the Environment

The microbiological monitoring program used during routine production and media fills should be described. The frequency of monitoring, type of monitoring, sites monitored, alert and action level specifications, and precise descriptions of the actions taken when specifications are exceeded should be included.

- Exceeded Limits - A description of the actions taken when environmental microbiological specifications are exceeded should be provided.

vii. Container-Closure and Package Integrity

The methods and results demonstrating the integrity of the microbiological barrier of the container-closure system should be summarized. This should include testing for initial validation. For initial validation of microbiological integrity of

container-closure systems, product sterility testing is not normally considered sufficient.

viii. Test Methods and Release Criteria

Product release tests for injectable products include sterility and pyrogenicity (or endotoxins) assessments as prescribed in 21 CFR 211.167(a). However, 21 CFR 211.165(a) permits the release of batches of drug composed of short-lived radiopharmaceuticals prior to the completion of sterility and pyrogen testing, but requires that such testing of each batch be started "as soon as possible." The laboratories performing these tests (particularly contract laboratories) should be identified and these should be in compliance with CGMP requirements.

- Sterility Test - Sterility test methods for [^{18}F]FDG will usually differ significantly from compendial test methods, so a clear description of the test should be provided. Procedures should be described and include the protocol for the selection of samples for testing. Testing performed within barrier systems should be discussed, and information concerning validation of the barrier system may be necessary.

- Bacterial Endotoxins Test and Method - Describe the bacterial endotoxins test for the product. This description should include qualification of the laboratory, inhibition, and enhancement testing and results, determination of noninhibitory concentration and maximum valid dilution. For further information see the agency guidance entitled *Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices*.

ix. Evidence of Formal Written Procedures

Evidence should be provided that there are formal, written procedures describing the above elements. Such evidence may consist of standard operating procedures (SOPs), or a listing of SOPs or protocols submitted as part of the elements listed above.

d. Maintenance of Microbiological Control and Quality: Stability Considerations

Due to the extremely short period of use for FDG-F18, stability considerations with regard to microbiological quality are greatly abbreviated.

L. In-Process Controls

1. In-Process Controls

A description of any in-process controls should be provided. Examples of procedures that may be performed are the yields of fluoride ions (in mCi), temperature of the reaction vessel, gas pressure and/or flow rate, and synthesis time. In certain automated units, it may not be possible to directly monitor certain in-process parameters. In this case, it should be so stated.

2. Copy of Executed Batch Record

An executed batch record for a representative batch should be submitted. The following information should be included in accordance with 21 CFR 314.50(d)(1)(ii)(b):

- The specifications and test procedures for each component and for the drug product;
- Names and addresses of all facilities involved in manufacturing, processing, packaging, and testing of the drug product and identification of the operation performed by each facility;
- The name and address of the supplier of the container/closure system;
- The results (primary data) of any tests performed on the components of the drug product, as required by 21 CFR 211.165.

Applicants should note that although records for other batches (validation and/or stability) used to support the application, need not be included in the submission, additional information on these may be requested during the review process. Batch records for all the batches used to support the application should be available on site for inspection.

M. Labeling Procedures

The procedure for labeling of the drug product should be described.

N. Container

The following information regarding the container/closure should be provided:

- Name and full address of the manufacturer of the container/closure system or individual components. Appropriate DMF reference(s), if any, and the letter(s) of authorization (LOA) should be included in the ANDA;
- Container glass type (refer to USP chapter <661>); Composition of the stopper and crimp seal (e.g., aluminum);
- Physical description (e.g., size, shape, volume, product catalog number);
- Container/closure compatibility, including leaching
- Acceptance specifications and tests performed.

O. Controls for the Finished Dosage Form

For general information on controls for the drug product, refer to the *Guideline for Submitting Documentation for the Manufacture and Controls for Drug Products*

1. Sampling Procedures

If multiple vials are manufactured, a sampling plan should be provided to assure that the test sample of the drug product is representative of the entire batch. However, if only one vial is manufactured, the description of the sampling procedure should be limited to the amount (volume) that is withdrawn from the final container and how it is distributed among the individual tests.

2. Regulatory Specifications, Methods, and Testing Schedules

The application should provide a list of specifications and identify the test methods (by name and code number) used to control the identity, strength, quality, and purity of the drug product. A schedule for performing each proposed test (i.e., pre or post release, frequency of testing) should be included. For [^{18}F]FDG, applicants should refer to section P "Analytical Methods" below for a list of tests that may satisfy the relevant identity, strength, quality, and purity criteria.

P. Analytical Methods

In this section, full details of the analytical test methods should be provided. The

following is a list of tests and schedules which, in the current opinion of the Agency, satisfy the identity, strength, quality, and purity criteria for the drug product.

1. Appearance

The test method and specifications for the appearance of the drug product should provide insurance that the drug product is clear, colorless, and free of particulate matter. This may be accomplished by visualization of the drug product through leaded glass. If, due to radiation safety considerations, the ability to visually inspect [^{18}F]FDG is limited, one acceptable approach is to incorporate procedures to provide that: (1) each component or container-closure system is inspected individually for visual evidence of particulate, foreign matter, and container-closure defects immediately before use; (2) defective components will not be used; and (3) the batch production and control record of the [^{18}F]FDG includes a signed or initialed verification that such inspection was conducted and that only acceptable finished articles were used.

2. Identity Tests(s)

Test methods and specifications for the radionuclidic and radiochemical identity of the drug product should be described.

a. Radionuclidic

The radionuclidic identity should be established on every batch of the drug product by the method described in the USP monograph for Fludeoxyglucose F18 Injection.

b. Radiochemical

The radiochemical identity may be established by a chromatographic procedure by comparing the radioactive drug product with the well characterized nonradioactive 2-deoxy-2-fluoro-D-glucose reference standard in a procedure such as HPLC or TLC. The radiochemical identity test should be performed on every batch of the drug product prior to its release.

3. Assay (Radioconcentration)

Specifications (range), in mCi/mL, and the method of determination of radioconcentration of the drug product should be described. The method should

clearly describe the procedure used for the determination of total radioactivity and the procedure used for the determination of the final volume in the container. This test should be performed on every batch of the drug product prior to its release.

4. Specific Activity

For [^{18}F]FDG, if a no-carrier added synthetic route is used, the specific activity need not be determined on a routine basis provided it is validated. Validation requires that the applicant of provide a drug product with consistent specific activity that at least meets the USP monograph requirements.

5. Purity

a. Radiochemical Purity

Specification and test method(s) for the radiochemical purity of the drug product should be described. A test method based on USP Fludeoxyglucose F18 Injection monograph may be acceptable. The radiochemical purity test method should be specific for Fludeoxyglucose F18. Applicants should demonstrate that the radioactivity associated with potential radiochemical impurities does not interfere with the measurement of radioactivity peak associated with Fludeoxyglucose F18. The radiochemical purity test should be performed on every batch of the drug product prior to its release.

b. Stereoisomeric Purity

In synthetic methods, where there is a possibility of formation of a stereoisomeric impurity (e.g., contamination of α and β anomers of fluorodeoxymannose in the electrophilic substitution synthesis method), a specification and a test method for the stereoisomeric purity should be provided. The drug product should meet the USP Fludeoxyglucose F18 Injection monograph for stereoisomeric purity requirements.

c. Radionuclidic Purity

Specifications for the radionuclidic purity and method for its determination should be described. The test method described in the USP monograph may be used. With acceptable validation, the radionuclidic purity test may be performed after release of the drug

product on the day of manufacture.

d. Chemical Purity

This drug product may be manufactured using different synthetic routes and processes and, therefore, may contain different impurities. Specifications, suitable methods, and schedules of testing for each impurity should be provided in the application. For example, if an applicant uses the Fludeoxyglucose F18 synthesis described by Hamacher et.al. [J. Nucl. Med. 27, 235-238 (1986)], then the residual amounts of kryptofix and the organic solvents employed in its manufacture may need to be monitored prior to the release of every batch of the drug product. Levels of other chemical impurities that may be found in the drug product (e.g., 2-chloro-2-deoxy-D-glucose) should be determined.

6. Pharmaceutical Quality

a. pH

A specification and the method of determination of pH of the drug product should be provided. The pH test should be performed prior to the release of every batch of the drug product. A pH paper test method may be acceptable, if performed using the reference standards at the lower and the upper range (with some allowance for the inaccuracy of the method) of the specifications. Applicants should note that during the shelf life, the pH of the drug product must remain within the proposed limits.

b. Osmolarity

Applicants should provide information that [^{18}F]FDG will yield a reproducible osmolarity.

c. Membrane Filter Integrity Test

The integrity of the membrane filter used to sterilize the radiochemical product should be assessed prior to the release of the drug product. The test method and specifications should be provided in the application. The bubble point measurement method may be used to test the membrane filter integrity.

d. Bacterial Endotoxin Testing

The test should be performed on every batch.

e. Sterility Testing

The test should be performed on every batch.

7. Method Validation

The applicant should only submit those methods in the method validation package that are non USP methods.

Q. Stability of Finished Dosage Form[3]

1. Selection and Number of Batches

Where a 60 minute irradiation time is employed, a single stability batch will suffice. Where a range of irradiation times are employed, three additional batches of the drug product manufactured at the upper end should be studied.

2. Proposed Expiration Dating Period

An expiration dating period for the drug product, based on its stability, should be proposed in the application. The drug product should meet all specifications at expiry.

3. Test Procedures

Full testing should be performed at the initial time point (i.e., at release) and at the expiry period. Because of the short expiration dating period, the sterility and bacterial endotoxin testing need only be performed at release.

4. Storage Conditions

Stability studies should be performed in the same container/closure system and

[3] The ICH Q1A guideline, *Stability Testing of New Drug Substances and Products*, and the *Guideline for Submitting Documentation For the Stability of Human Drugs and Biologics* (Stability Guidance) provide broad guidance in designing the stability studies for drug products.

at the same temperature in which the drug product will be stored during its shelf life (e.g., the drug product vial). The vial should be stored in the inverted position during the stability study.

5. Analytical Results on Stability Batch

The stability study analytical results should be provided in the application. Relevant information should include batch number, date of manufacture, storage condition, vial position, total radioactivity, and radioconcentration.

6. Postapproval Stability Protocol

The first three production batches are to be placed on the stability protocol. After the marketing approval of an ANDA, one production batch per year should be placed on the stability protocol.

R. Samples

If the analytical methods are to be validated in FDA laboratories, the applicant will be notified when samples should be provided. See also 21 CFR 314.94(a)(10) and 21 CFR 314.50(e)(1) and (e)(2)(i).

S. Other Information

Copies of cited references, their English translation (if not in English), and letters of authorization must be included as part of the other information in the application (21 CFR 314.50(g)(1) and (2)).

IV. REFERENCES[4]

Letters to Industry

October 31, 1986, letter to all NDA and ANDA holders and applicants on patent issues and the three-year exclusivity provisions.

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[4]The reference documents are available from the Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; (tel) 301-827-4573.

April 28, 1988, letter from the Director, Center for Drug Evaluation and Research, to all NDA and ANDA holders and applicants on the Drug Price Competition and Patent Term Restoration Act of 1984. The letter focuses on the three- and five-year exclusivity provisions.

July 29, 1988, letter from the Director, Center for Drug Evaluation and Research, to industry on the Drug Price Competition and Patent Term Restoration Act of 1984.

November 8, 1991, letter from the Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to industry on improving the efficiency and effectiveness of the generic drug review process.

July 27, 1992, letter from the Deputy Commissioner for Operations to drug manufacturers/industry associations on the 1992 Generic Drug Enforcement Act, specifically on debarment certification and convictions statements.

January 15, 1993, letter from the Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to all ANDA and AADA applicants regarding refusal to file and refusal to approve incomplete applications based on the new requirements of the 1992 Generic Drug Enforcement Act.

August 4, 1993, letter from the Acting Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to industry providing information on labeling, scale-up, packaging, minor/major amendment criteria, and bioequivalence requirements.

April 8, 1994, letter from the Acting Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to all ANDA and AADA applicants on a variety of application-related issues. This letter also contains a list of industry questions and Agency answers resulting from the August 4, 1993, letter to industry.

October 14, 1994, letter from the Director, Center for Drug Evaluation and Research and the Associate Commissioner for Regulatory Affairs to all NDA, ANDA, and AADA applicants on the roles of CDER chemistry review scientists and Office of Regulatory Affairs field investigators.

Guidance Documents

International Conference on Harmonisation. 1994. *Stability Testing of New Drug Substances and Products*, ICH-Q1A, September 1994.

U.S. Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER) and Center for Veterinary Medicine (CVM). 1994. *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*, November 1994.

DHHS, FDA. 1987. *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics*, February 1987.

DHHS, FDA. 1987. *Guideline for Submitting Documentation for the Manufacture and Controls for Drug Products*, February 1987.

DHHS, FDA, CDER. *Approved Drug Products With Therapeutic Equivalence Evaluations.*

DHHS, FDA, CDER, Office of Compliance. 1987. *Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices,* November 1987.

DHHS, FDA, CDER, Office of Generic Drugs. 1997. *Fludeoxyglucose F18 Injection Labeling Guidance*, January 1997.

DHHS, FDA, CDER, Office of Generic Drugs. 1994. *Interim Inactive Ingredients Policy*, November 17, 1994.

DHHS, FDA, CDER, Office of Management. *Inactive Ingredient Guide.*

DHHS, FDA, CDER. 1997. *Guidance for Industry: Organization of an Abbreviated New Drug Application (ANDA) and an Abbreviated Antibiotic Application (AADA)*, April 1997.

above, pursuant to 5 U.S.C. 553(b)(B), notice and public procedure are unnecessary. Since this document is not subject to the notice and public procedure requirements of 5 U.S.C. 553, it is not subject to the provisions of the Regulatory Flexibility Act (5 U.S.C. 601 *et seq.*). Further, this document does not meet the criteria for a "significant regulatory action" as specified in Executive Order 12866.

List of Subjects in 19 CFR Part 133

Copyrights, Counterfeit goods, Customs duties and inspection, Imports, Penalties, Prohibited merchandise, Reporting and recordkeeping requirements, Restricted merchandise, Seizures and forfeitures, Trademarks, Trade names, Unfair competition.

Amendment to the Regulations

For the reasons stated above, part 133 of the Customs Regulations (19 CFR part 133) is amended as set forth below:

PART 133—TRADEMARKS, TRADE NAMES, AND COPYRIGHTS

1. The general authority citation for part 133 continues to read as follows:

Authority: 17 U.S.C. 101, 601, 602, 603; 19 U.S.C. 66, 1624; 31 U.S.C. 9701.

* * * * *

§ 133.42 [Amended]

2. In § 133.42, the third sentence of paragraph (c) is amended by removing the words ", unless the article may be returned to the country of export as provided in § 133.47".

§ 133.44 [Amended]

3. In § 133.44, the first sentence of paragraph (a) is amended by removing the word "either" and the words "or, if the conditions prescribed by § 133.47 are met, permit the importer to return the article to the country of export". In the last sentence, the words "In either event, the" are removed and the word "The" is added in their place.

§ 133.47 [Removed]

4. Section 133.47 is removed.

Samuel H. Banks,

Acting Commissioner of Customs.

Approved: March 24, 1997.

John P. Simpson,

Deputy Assistant Secretary of the Treasury.

[FR Doc. 97-10272 Filed 4-21-97; 8:45 am]

BILLING CODE 4820-02-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 5

Delegations of Authority and Organization

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending regulations for delegations of authority to allow the Director of the Center for Drug Evaluation and Research (CDER) and the Director of the Office of Compliance, CDER, to grant or deny a request, submitted in the form of a citizen petition under its pertinent regulations, for an exception or alternative to applicable current good manufacturing practice (CGMP) requirements for positron emission tomography (PET) drug products. This action is necessary to allow CDER to be able to grant an exception or alternative to applicable CGMP requirements for PET drug products when the request is made in a citizen petition.

EFFECTIVE DATE: April 28, 1997.

FOR FURTHER INFORMATION CONTACT:

Robert K. Leedham, Center for Drug Evaluation and Research (HFD-343), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1026, or

Donna G. Page, Division of Management Systems and Policy (HFA-340), Food and Drug Administration, 5600 Fishers Lane, Rockville MD 20857, 301-827-4816.

SUPPLEMENTARY INFORMATION: A final rule providing the Director and the Director of the Office of Compliance, CDER, with the authority to grant requested exceptions and alternatives to requirements in 21 CFR part 211 pertaining to CGMP's for PET radiopharmaceutical drug products is published elsewhere in this issue of the **Federal Register**. This delegation allows these two agency officials to grant or deny such requests when submitted in the form of a citizen petition under 21 CFR 10.30.

Further redelegation of the authorities delegated is authorized. Authority delegated to a position by title may be exercised by a person officially designated to serve in such position in an acting capacity or on a temporary basis.

List of Subjects in 21 CFR Part 5

Authority delegations (Government agencies), Imports, Organization and functions (Government agencies).

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority of the Commissioner of Food and Drugs, 21 CFR part 5 is amended as follows:

PART 5—DELEGATIONS OF AUTHORITY AND ORGANIZATION

1. The authority citation for 21 CFR part 5 continues to read as follows:

Authority: 5 U.S.C. 504, 552, App. 2; 7 U.S.C. 138a, 2271; 15 U.S.C. 638, 1261-1282, 3701-3711a; secs. 2-12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451-1461); 21 U.S.C. 41-50, 61-63, 141-149, 467f, 679(b), 801-886, 1031-1309; secs. 201-903 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321-394); 35 U.S.C. 156; secs. 301, 302, 303, 307, 310, 311, 351, 352, 361, 362, 1701-1706, 2101 of the Public Health Service Act (42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 264, 265, 300u-300u-5, 300aa-1); 42 U.S.C. 1395y, 3246b, 4332, 4831(a), 10007-10008; E.O. 11490, 11921, and 12591.

2. Section 5.31 is amended by adding new paragraph (h) to read as follows:

§ 5.31 Petitions under part 10.

* * * * *

(h) The Director and the Director of the Office of Compliance, CDER, are each authorized to grant or deny citizen petitions submitted under § 10.30 of this chapter requesting an exception or alternative to any requirement in part 211 of this chapter pertaining to current good manufacturing practice for positron emission tomography radiopharmaceutical drug products.

Dated: April 15, 1997.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 97-10340 Filed 4-21-97; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 211

[Docket No. 94N-0421]

RIN 0910-AA45

Current Good Manufacturing Practice for Finished Pharmaceuticals; Positron Emission Tomography

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations to permit FDA to approve requests from manufacturers of positron emission tomography (PET) radiopharmaceutical drug products for exceptions or alternatives to provisions of the current good manufacturing practice (CGMP) regulations. This action is intended to relieve manufacturers of PET radiopharmaceutical drug products from regulations that might result in unsafe handling of these products or that are inapplicable or inappropriate, and that do not enhance safety or quality in the manufacture of PET radiopharmaceutical drug products. Elsewhere in this issue of the **Federal Register**, FDA is amending its regulations to authorize the Director, Center for Drug Evaluation and Research (CDER) and CDER's Director of the Office of Compliance to grant or deny citizen petitions under FDA regulations requesting an exception or alternative to any requirement pertaining to CGMP.

EFFECTIVE DATE: April 28, 1997.

ADDRESSES: Decisions on the petitions may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Robert K. Leedham, Center for Drug Evaluation and Research (HFD-343), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1026.

SUPPLEMENTARY INFORMATION:

I. Background

PET is a medical imaging modality used to assess the body's biochemical processes. Radionuclides are manufactured into PET radiopharmaceutical drug products that are then administered to patients for medical imaging. The medical images of the body's biochemical processes are then evaluated, generally for diagnostic purposes.

PET radiopharmaceutical drug product manufacturing differs in a number of important ways from the manufacture of conventional drug products:

1. Because of the short physical half-lives of PET radiopharmaceutical drug products, PET facilities generally manufacture the products in response to daily demand for a relatively small number of patients.

2. Manufacturing may be limited and only a few lots are produced each day.

3. PET radiopharmaceutical drug products must be administered to patients within a short period of time after manufacturing because of the short physical half-lives of the products.

In the **Federal Register** of February 27, 1995 (60 FR 10517), FDA proposed to permit manufacturers of PET radiopharmaceutical drug products to apply to the agency for approval of exceptions or alternatives to the requirements of the CGMP regulations in part 211 (21 CFR part 211). The agency noted in the proposal that there are fundamental principles of the CGMP regulations that must be applied to drug manufacturing processes, including those for PET radiopharmaceutical drug products, to ensure the safety and efficacy of the finished products. However, part 211 is primarily directed to regulating the manufacture of conventional, nonradioactive drug products, and there are certain aspects of the manufacture of PET radiopharmaceutical drug products that are unique. Therefore, regulations in part 211 may contain requirements that could result in unsafe handling or that are inapplicable or inappropriate to the manufacture of PET radiopharmaceutical drug products and do not otherwise enhance drug product quality.

The proposal specified that a request for an exception would be required to contain an explanation of why compliance with a particular CGMP provision is unnecessary or cannot be achieved. It also specified that a request for an alternative would be required to contain an explanation of how a proposed alternative procedure would satisfy the purpose of the CGMP requirement. The proposal stated that either the Director of CDER or CDER's Director of the Office of Compliance could approve an exception or alternative if it is determined that: (1) The requestor's compliance with the requirement is unnecessary to protect the radiopharmaceutical drug product's quality or safety; (2) the proposed alternative procedures satisfy the purpose of the CGMP requirement; or (3) the requestor's submission otherwise justified an exception or alternative. In addition, the proposal would allow either CDER's Director or CDER's Director of the Office of Compliance to withdraw the approval of an exception or alternative by issuing a written notice to the requestor who had obtained approval for the exception or alternative.

The proposed rule was one of three documents dealing with PET radiopharmaceutical drug products that FDA published in the **Federal Register** of February 27, 1995. Another document announced the availability of a draft guideline on the manufacture of PET radiopharmaceutical drug products (60 FR 10593). The third document announced a March 21, 1995, public workshop and explained the applicable statutory and regulatory requirements for these products (60 FR 10594). This final rule pertains only to the exceptions and alternatives to CGMP regulations for PET radiopharmaceutical drug products and addresses only those comments received on this issue.

This final rule will become effective 5 days after the date of publication in the **Federal Register**. This final rule is a substantive rule which, in the discretion of the agency, grants or recognizes an exemption or relieves a restriction. (See 5 U.S.C. 553(d)(1) and § 10.40(c)(4)(i) (21 CFR 10.40(c)(4)(i).) In addition, the Commissioner of Food and Drugs finds good cause for making a final rule, based on the proposal, effective 5 days after the date of publication in the **Federal Register**. (See 5 U.S.C. 553(d)(3) and § 10.40(c)(4)(ii).) The manufacturing process for PET radiopharmaceutical drug products is sufficiently different from that of other regulated products that application of certain CGMP requirements to the PET manufacturing process may be impractical. Because PET radiopharmaceutical drug products are already in use, a later effective date may delay FDA approval of exceptions or alternatives or hinder appropriate application of the CGMP regulations necessary to protect the integrity of the PET radiopharmaceutical manufacturing process.

II. Comments on the Proposed Rule

FDA gave interested persons until March 29, 1995, to comment on the proposed rule. The agency received comments from pharmaceutical manufacturers, health professionals, professional organizations, and State regulatory agencies. A summary of these comments and FDA's responses follows.

A. Application of CGMP Regulations to PET Radiopharmaceutical Drug Products

Several comments questioned the need to apply CGMP regulations to PET radiopharmaceutical drug products. One comment stated that there had not been an adequate explanation of why PET radiopharmaceutical drug products needed to be governed by CGMP regulations. Several comments suggested alternative standards for the regulation of PET radiopharmaceutical drug products such as the United States Pharmacopeia, the American Pharmaceutical Association Practice Standards for PET Nuclear Pharmacists, or standards set by State boards of pharmacy. Another comment suggested that FDA, in conjunction with the PET

radiopharmaceutical community, develop a regulation specifically for PET radiopharmaceutical drug products.

This rule does not trigger the applicability of CGMP regulations. CGMP regulations apply to PET radiopharmaceutical drug products by virtue of the fact that, under section 201(g) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(g)), these products are drugs and are, therefore, subject to the drug provisions of the act. In a notice published in the **Federal Register** of February 27, 1995 (60 FR 10594 at 10595), FDA reiterated this fact concerning the regulation of PET radiopharmaceutical drug products. Under section 501(a)(2)(B) of the act (21 U.S.C. 351(a)(2)(B)), drugs are deemed adulterated unless manufactured in conformity with CGMP requirements. PET radiopharmaceutical drug products are subject to each of the adulteration provisions of the act, including CGMP requirements, even if they are prepared in pharmacies or by pharmacists. (See *Professionals & Patients for Customized Care* v. *Shalala*, 847 F. Supp. 1359, 1364 (S.D. Tex. 1994), *aff'd*, 56 F.3d 592 (5th Cir. 1995).) Therefore, all PET radiopharmaceutical drug products must be manufactured in compliance with CGMP regulations. The regulations in part 211 contain minimum manufacturing practices to be followed by manufacturers of all drug products. Thus, in the absence of this rule, all CGMP requirements would apply to the manufacturing of PET drug products.

FDA's experience has shown that the CGMP regulations are flexible enough to accommodate most drug products and that it is generally unnecessary to create specific CGMP regulations for particular classes of drug products. Such regulations would necessarily contain a large number of provisions identical to, and redundant with, those already present in part 211. Where a CGMP regulation has been shown to be unnecessary or does not enhance the safety or quality of the manufacturing process for certain drug classes, FDA has revised the application of that regulation for that class. For example, in the **Federal Register** of November 28, 1980 (45 FR 79089), FDA amended § 211.170 to reduce the time that manufacturers are required to retain reserve samples of radioactive drugs and to exempt such drugs from the requirement for annual visual examination of reserve samples.

Although the fundamental principles embodied in the CGMP regulations are applicable to the PET radiopharmaceutical drug product manufacturing process, there are certain provisions that may not apply because of unique manufacturing characteristics. As a result, this final rule permits FDA to allow exceptions or alternatives to the CGMP regulations for PET radiopharmaceutical drug products. In addition, FDA is considering making further revisions to part 211, through rulemaking including adding a new subpart to the CGMP regulations to deal with exceptions or alternatives applicable to all PET radiopharmaceutical drug products.

B. Exceptions and Alternatives to CGMP Regulations

Several comments criticized FDA's proposed procedures to receive and evaluate requests for exceptions or alternatives to the CGMP regulations for PET radiopharmaceutical drug products. The comments objected to the proposed requirement that each manufacturer must separately describe and justify each proposed specific exception or alternative. One comment stated that FDA should identify those specific CGMP provisions from which all PET manufacturers could generally be excepted. Another comment stated that excepting some PET radiopharmaceutical drug manufacturers and not others might cause problems. A third comment stated that it is important that any alternatives and exceptions be made public and that the CGMP regulations be applied consistently and equally to all PET radiopharmaceutical drug manufacturing centers.

At this time, FDA believes that it is necessary to review individualized requests to determine whether exceptions or alternatives to CGMP regulations requested for PET radiopharmaceutical drug product manufacturing are consistent with the basic principles of the CGMP regulations and whether differences in existing PET manufacturing techniques, or the volume of product produced, may have an impact on product quality. Any procedure used in the manufacture of PET radiopharmaceutical drug products must provide a reasonable degree of certainty that products will be manufactured with consistent quality. The agency will periodically provide guidance to industry on the application of the CGMP regulations to PET radiopharmaceutical drug products.

FDA agrees that it is important that exceptions and alternatives be applied consistently to all PET radiopharmaceutical drug product manufacturers. To promote such consistency, FDA has withdrawn the provision in proposed § 211.1(d) that would have, under certain circumstances, expressly allowed oral requests for exceptions and alternatives and also would have allowed FDA to issue oral decisions on such requests. The agency believes that it is important to keep written records to maintain consistency, to adequately evaluate requests for exceptions and alternatives, and to prevent misunderstandings.

FDA also agrees that information on exceptions and alternatives should be publicly available. To maintain a publicly available record of requests for exceptions and alternatives, and agency action on such requests, FDA believes that exceptions and alternatives should be submitted in the form of a citizen petition under § 10.30 (21 CFR 10.30). A request for an exception or alternative should be clearly identified as a "PET Request for Exception or Alternative to the CGMP Regulations." Decisions with respect to such petitions will be maintained for public review in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Elsewhere in this issue of the **Federal Register**, FDA is amending 21 CFR 5.31 to authorize the Director of CDER and CDER's Director of the Office of Compliance to grant or deny citizen petitions under § 10.30 requesting an exception or alternative to any requirement in part 211 pertaining to CGMP for PET radiopharmaceutical drug products.

The proposed rule specifically listed elements that would be required to be included in a request for exception or alternative and also specifically listed the factors pertaining to FDA's decision whether to grant such a request. In response to comments that the procedure in the proposed rule was too burdensome, the final rule provides greater flexibility in that it does not require that any particular element be included in a request for exception or alternative, and does not narrowly constrain FDA's discretion to grant such a request.

Although the codified language of the regulation no longer contains specific required elements, the agency expects that a citizen petition requesting an exception or alternative would be approved if the agency determined, based upon a request, including supporting data as necessary, that: (1) The requestor's compliance with the CGMP requirement is unnecessary to provide suitable assurance that the drug meets the requirements of the act as to safety and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess, or compliance with the requirement is not possible to

achieve: (2) alternative procedures or controls suggested and sufficiently described by the requestor satisfy the purpose of the requirement; or (3) the requestor's submission otherwise justifies an exception or alternative. Although no longer specified in the regulation, these factors, pertaining to FDA's decisions on requests for exceptions and alternatives, provide guidance both to assist PET manufacturers in preparing requests and to assist FDA in consistently evaluating those requests. As further guidance, citizen petitions for an exception or alternative may be submitted by manufacturers or trade associations individually or as a group, as long as the facts presented are sufficiently individualized for each manufacturer seeking the exception or alternative.

C. Usefulness of the Rule

Several comments objected to the proposed provision for requesting an exception or alternative to the CGMP regulations, arguing that it would not likely achieve its goal of reducing the burden on PET radiopharmaceutical drug products and would not be cost-effective.

FDA disagrees with these comments. As explained above, the purpose of the rule is to relieve PET radiopharmaceutical drug product manufacturers from regulatory provisions that might result in unsafe handling of PET radiopharmaceutical drug products, that are inapplicable or inappropriate, or that do not enhance the safety or quality of PET radiopharmaceutical drug products. The agency believes that, with the added flexibility provided by this final rule, the CGMP regulations can be applied to PET radiopharmaceutical drug products in a way that accommodates their unique manufacturing aspects while still protecting the integrity of the manufacturing process. The agency will continue to work with these manufacturers in an effort to apply CGMP requirements to PET radiopharmaceutical drug products in ways that are practical and achievable.

III. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(10) 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.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule is expected to have a significant economic impact on a substantial number of small entities, the agency must analyze regulatory options that would minimize any significant economic impact of the rule on small entities. The Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an annual expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more (annually adjusted for inflation).

The agency has reviewed this final rule and has determined that the rule is consistent with the principles set forth in the Executive Order. FDA finds that the rule is not a significant regulatory action under the Executive Order. In addition, the agency finds that the rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in an annual expenditure of $100 million or more.

The fact that PET radiopharmaceuticals are drugs requires compliance with the CGMP requirements under section 501(a)(2)(B) of the act, and all finished pharmaceuticals are subject to the requirements imposed by the CGMP regulations set forth in this part. This rule will allow FDA to approve requests from manufacturers of PET radiopharmaceutical drug products for exceptions or alternatives to the CGMP requirements as they apply to the unique characteristics of PET radiopharmaceutical drug product manufacturing, without compromising CGMP standards that are necessary to meet the CGMP requirements.

FDA estimates that there are approximately 70 facilities that manufacture PET radiopharmaceutical drug products, and the agency assumes for the purposes of this analysis that each facility is a small entity within the meaning of the Regulatory Flexibility Act. The only costs associated with this rule are the possible costs associated with requesting an exception or alternative.

FDA estimates that it will take approximately 20 hours, or less, for each facility to develop its request for exceptions or alternatives. Assuming that each of the 70 facilities submits one request, the burden would total 1,400 hours. Using the 1995 median weekly earnings of $524[1] for clinical laboratory technologists and technicians, and adding 40 percent for fringe benefits, the average hourly earnings would be $18.34. Thus, the combined costs for all facilities would total less than $26,000. FDA concludes that these incidental one time costs of approximately $367 per facility would constitute an insignificant percentage of gross revenue, even for a small entity.

In addition, it is expected that some facilities will collaborate with each other, or with trade associations, to submit bundled requests, as long as the facts presented are sufficiently individualized for each manufacturer seeking the exception or alternative. Moreover, because the filing of a request for an exception or alternative is voluntary, it is unlikely that a facility will file such a request unless it expects the benefit derived to exceed the cost of preparing and filing the request. Consequently, FDA believes that the rule will, in fact, provide a net economic savings for each facility that chooses to request an exception or alternative to a CGMP requirement. Therefore, under the Regulatory Flexibility Act, 5 U.S.C. 605(b), the Commissioner of Food and Drugs certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

List of Subjects in 21 CFR Part 211

Drugs, Labeling, Laboratories, Packaging and containers, Prescription drugs, Reporting and recordkeeping requirements, Warehouses.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 211 is amended as follows:

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

1. The authority citation for 21 CFR part 211 continues to read as follows:

Authority: Secs. 201, 501, 502, 505, 506, 507, 512, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 355, 356, 357, 360b, 371, 374).

2. Section 211.1 is amended by adding new paragraph (d) to read as follows:

[1] Employment and Earnings, U.S. Department of Labor, Bureau of Labor Statistics, vol. 43, No. 1, p. 206, January 1996

§ 211.1 Scope.

* * * * *

(d)(1) The Director of the Center for Drug Evaluation and Research (CDER) and the CDER Director of the Office of Compliance each may approve a request from a manufacturer of positron emission tomography (PET) drug products for an exception or alternative to any requirement of this part pertaining to current good manufacturing practice for PET drug products.

(2) An approval under paragraph (d)(1) of this section may be withdrawn if either Director finds that such exception or alternative is no longer justified. Withdrawal of such approval shall be accomplished by providing written notice of such withdrawal, and the reasons for the withdrawal, to the original requestor.

Dated: April 15, 1997.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 97-10341 Filed 4-21-97; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF THE INTERIOR

Minerals Management Service

30 CFR Part 218

RIN 1010-AC01

Amendments to Regulations Governing Collection of Royalties, Rentals, Bonuses, and Other Monies Due the Federal Government

AGENCY: Minerals Management Service (MMS), Interior.

ACTION: Final rulemaking.

SUMMARY: MMS is amending its regulations that specify how payments are made for mineral lease royalties, rentals, and bonuses. The changes are needed to incorporate revised U.S. Treasury requirements. Also, MMS has clarified language for other parts of this regulation.

DATES: Effective date May 22, 1997.

FOR FURTHER INFORMATION CONTACT: David S. Guzy, Chief, Rules and Procedures Staff, phone (303) 231-3432, FAX (303) 231-3194, e-Mail David_Guzy@smtp.mms.gov.

SUPPLEMENTARY INFORMATION: The principal authors of this rule are David J. Menard of the Reports and Financial Division, Financial Branch, Jim McNamee of the Office of Policy and Management Improvement, and David S. Guzy of the Rules and Procedures Staff, Lakewood, Colorado.

I. Background

The purpose of this final rule is to comply with the U.S. Treasury's final rule amending 31 CFR Part 206, Management of Federal Agency Receipts, Disbursements, and Operation of the Cash Management Improvement Fund (59 FR 4536, 1/31/94). That rule requires executive agencies to use effective, efficient disbursement mechanics, principally Electronic Funds Transfer (EFT), in making their payments. That rule also requires executive agencies to use EFT for collecting funds.

MMS has written this rule in plain English.

II. Comments on Proposed Rule

MMS published a proposed rule on April 19, 1996, at 61 FR 17267. The proposed rulemaking provided for a 60-day comment period, which ended June 18, 1996, and was extended to July 19, 1996, by a **Federal Register** Notice (61 FR 28829, June 6, 1996).

General Comments

Commenters believe writing the rule in plain English improves clarity and makes the rule easier to understand. Commenters stated they will continue to work with MMS to identify the most efficient and practical way to make payments to MMS.

Response. We appreciate these comments and will continue the plain English concept in all future rulemakings.

Specific Comments

Comment on § 218.51(a). One commenter did not think it is necessary to define person or payment when used in their common or ordinary meaning.

Response. MMS has determined that these definitions lend clarity and conform with other MMS rules. No change will be made in the final rule.

Comment on § 218.51(b). The same commenter pointed out that the word *general* was misspelled.

Response. We will correct the spelling in the final rule.

Comment on § 218.51(b)(1). Five commenters responded as follows:

(1) The section is vague and arbitrary. Sentence is circular and describes a discretionary standard. As written, the payer must use EFT anytime MMS requires EFT regardless of the reasoning or criteria or basis for the decision. They suggested alternative language.

(2) The requirement is in conflict with the preamble. Their opinion is that making all payments by EFT is neither cost effective nor practicable. They said many Indian payments cost more to process than the invoice they are paying and adding the cost of making these payments by EFT would not be cost effective. They recommend a threshold of $10,000.

(3) They feel there is a conflict with § 218.51(b) which says "to the extent it is cost effective and practicable," and this section which says if instructed you must pay by EFT. They recommend a threshold of $10,000.

(4) They feel the statement of "If MMS instructs you to use * * *." conflicts with the general spirit of the preamble. They feel the additional cost of making EFT payments is not justifiable from the company standpoint. They recommend the $10,000 limit be maintained.

(5) They do not believe the additional cost of making EFT payments is justifiable from the company standpoint. They recommend retaining the current $10,000 threshold.

Response. MMS does not intend to be arbitrary in implementing the Treasury EFT requirement. The Treasury rule does not allow for any type of stated threshold. Our elimination of the threshold is based on Treasury's requirement that we increase our efficiency in collecting Government monies. We feel the new rule is consistent with the Treasury rule.

We are aware of the cost and technical issues associated with making EFT payments. The U.S. Treasury is working with the banking industry to broaden the use of EFT. MMS believes our record of working with payors in implementing EFT has not been arbitrary or burdensome. It has not been our policy nor will it be our policy to unduly burden industry with EFT payment requirements. As EFT becomes more widespread, the cost should decrease; therefore, EFT will be more beneficial to industry and the Government.

Comment on § 218.51(b)(3). One commenter stated that the paragraph is confusing and should be rewritten to clearly define intent. The commenter asked two questions: (1) "Does this statement mean that separate reports or report lines are required? (2) Are separate checks or separate lines on the check stub or other payment document needed?"

Response. The intent of this paragraph is to emphasize the fact that you must not mix Federal and Indian lease payments on a payment document. In other words, you must not include any Indian lease payments in your Federal payment documents or any Federal lease payments in your Indian payment documents. This proposed rule deals only with payments and does not change any reporting requirements.

Wilma G. Johnson,
Acting Associate Director for Policy Planning And Evaluation, Centers for Disease Control and Prevention (CDC).
[FR Doc. 97-10312 Filed 4-21-97; 8:45 am]
BILLING CODE 4163-18-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97F-0157]

Japan Vilene Co., Ltd.; Filing of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that Japan Vilene Co., Ltd., has filed a petition proposing that the food additive regulations be amended to provide for the safe use of 2-propenoic acid, polymer with 2-ethyl-2-(((1-oxo-2-propenyl)oxy)methyl)-1,3-propanediyl di-2-propenoate and sodium 2-propenoate (CAS Reg. No. 76774-25-9) as a fluid absorbent material intended for use in contact with food.

DATES: Written comments on the petitioner's environmental assessment by May 22, 1997.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Andrew J. Zajac, Center for Food Safety and Applied Nutrition (HFS-215), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-418-3095.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5) (21 U.S.C. 348(b)(5))), notice is given that a food additive petition (FAP 7B4537) has been filed by Japan Vilene Co., Ltd., c/o Center for Regulatory Services, 2347 Paddock Lane, Reston, VA 20191. The petition proposes to amend the food additive regulations to provide for the safe use of 2-propenoic acid, polymer with 2-ethyl-2-(((1-oxo-2-propenyl)oxy)methyl)-1,3-propanediyl di-2-propenoate and sodium 2-propenoate (CAS Reg. No. 76774-25-9) as a fluid absorbent material intended for use in contact with food.

The potential environmental impact of this action is being reviewed. To encourage public participation consistent with regulations promulgated under the National Environmental Policy Act (40 CFR 1501.4(b)), the agency is placing the environmental assessment submitted with the petition that is the subject of this notice on public display at the Dockets Management Branch (address above) for public review and comment. Interested persons may, on or before May 22, 1997, submit to the Dockets Management Branch (address above) written comments. 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 the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. FDA will also place on public display any amendments to, or comments on, the petitioner's environmental assessment without further announcement in the **Federal Register**. If, based on its review, the agency finds that an environmental impact statement is not required and this petition results in a regulation, the notice of availability of the agency's finding of no significant impact and the evidence supporting that finding will be published with the regulation in the **Federal Register** in accordance with 21 CFR 25.40(c).

Dated: April 1, 1997.

Alan M. Rulis,
Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.

[FR Doc. 97-10415 Filed 4-21-97; 8:45 am]
BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 94D-0422]

Guidance for Industry: Current Good Manufacturing Practices for Positron Emission Tomographic (PET) Drug Products; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance entitled "Guidance for Industry: Current Good Manufacturing Practices for Positron Emission Tomographic (PET) Drug Products" prepared by FDA's Center for Drug Evaluation and Research (CDER). The guidance is intended to assist persons involved in the production of PET radiopharmaceutical drug products in achieving compliance with FDA's current good manufacturing practice (CGMP) regulations for finished pharmaceuticals.

DATES: Persons may submit written comments on the guidance at any time.

ADDRESSES: Submit written requests for single copies of the guidance entitled "Guidance for Industry: Current Good Manufacturing Practices for Positron Emission Tomographic (PET) Drug Products" to the Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. An electronic version of this guidance is available via Internet using the World Wide Web (WWW). To connect to the CDER home page, type "http://www.fda.gov/cder" and go to the "Regulatory Guidance" section. Submit written comments on the guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. Requests and comments should be identified with the docket number found in brackets in the heading of this document. A copy of the guidance and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Robert K. Leedham, Center for Drug Evaluation and Research (HFD-343), Food and Drug Administration, 7520 Standish Pl., Rockville, MD 20855, 301-594-1026.

SUPPLEMENTARY INFORMATION: FDA is announcing the availability of a guidance entitled "Guidance for Industry: Current Good Manufacturing Practices for Positron Emission Tomographic (PET) Drug Products." PET is a medical imaging modality used to assess the body's biochemical processes. Radionuclides are manufactured into PET radiopharmaceutical drug products that are administered to patients for medical imaging. The images of the body's biochemical processes are then evaluated, generally for diagnostic purposes.

In the **Federal Register** of February 27, 1995 (60 FR 10593), FDA announced the availability of its "Draft Guideline on the Manufacture of Positron Emission Tomographic (PET) Drug Products." The notice gave interested persons an opportunity to submit comments by May 30, 1995. FDA received comments from more than 20 persons. The final PET CGMP guidance

contains revisions incorporating many of those comments.

The PET CGMP guidance discusses the requirements for manufacturing practices, procedures, and facilities used to prepare PET radiopharmaceuticals. The guidance addresses such matters as quality control units, personnel qualifications, staffing, buildings and facilities, equipment, components, containers, closures, production and process controls, packaging and labeling controls, holding and distribution, testing and release for distribution, stability testing and expiration dating, reserve samples, yields, second-person checks, reports, and records. The guidance focuses particular attention on CGMP requirements that are of special concern due to unique characteristics inherent in the production and control of PET radiopharmaceuticals.

PET radiopharmaceutical drug product manufacturing differs in a number of important ways from the manufacture of conventional drug products:

(1) Because of the short physical half-lives of PET radiopharmaceuticals, PET facilities generally manufacture the products in response to daily demand for a relatively small number of patients.

(2) Manufacturing may be limited and only a few lots produced each day.

(3) PET radiopharmaceuticals must be administered to patients within a short period of time after manufacturing because of the short half-lives of the products.

FDA recognized that, because of these differences, application of certain provisions of the CGMP regulations in part 211 (21 CFR part 211) to the manufacture of PET radiopharmaceuticals might result in unsafe handling or be otherwise inappropriate. Therefore, elsewhere in this issue of the **Federal Register**, the agency is publishing a final rule authorizing manufacturers of PET radiopharmaceuticals to apply to the agency for exceptions or alternatives to provisions of the CGMP regulations. The PET CGMP guidance notes that while the CGMP regulations apply to the manufacture of PET radiopharmaceuticals, new § 211.1(d) permits manufacturers of such drugs to request an exception or alternative to any requirement in part 211.

This guidance represents the agency's current thinking on CGMP's for PET radiopharmaceuticals. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. A regulated entity may adopt an alternative approach to CGMP's for PET drugs if such approach satisfies the requirements of the Federal Food, Drug, and Cosmetic Act and FDA regulations.

Interested persons may, at any time, submit to the Dockets Management Branch (address above) written comments on the guidance. If written comments demonstrate that changes to the final guidance are appropriate, FDA will revise the guidance accordingly. 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 guidance and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: April 15, 1997.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 97-10342 Filed 4-21-97; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). This notice also summarizes the procedures for the meeting and methods by which interested persons may participate in open public hearings before FDA's advisory committees.

FDA has established an Advisory Committee Information Hotline (the hotline) using a voice-mail telephone system. The hotline provides the public with access to the most current information on FDA advisory committee meetings. The advisory committee hotline, which will disseminate current information and information updates, can be accessed by dialing 1-800-741-8138 or 301-443-0572. Each advisory committee is assigned a 5-digit number. This 5-digit number will appear in each individual notice of meeting. The hotline will enable the public to obtain information about a particular advisory committee by using the committee's 5-digit number. Information in the hotline is preliminary and may change before a meeting is actually held. The hotline will be updated when such changes are made.

MEETING: The following advisory committee meeting is announced:

Endocrinologic and Metabolic Drugs Advisory Committee

Date, time, and place. May 14, 1997, 8 a.m., Holiday Inn—Bethesda, Versailles Ballrooms I and II, 8120 Wisconsin Ave., Bethesda, MD.

Type of meeting and contact person. Open public hearing, 8 a.m. to 9 a.m., unless public participation does not last that long; open committee discussion, 9 a.m. to 5 p.m.; Kathleen Reedy or LaNise Giles, Center for Drug Evaluation and Research (HFD-21), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-5455, or FDA Advisory Committee Information Hotline, 1-800-741-8138 (301-443-0572 in the Washington, DC area), Endocrinologic and Metabolic Drugs Advisory Committee, code 12536. Please call the hotline for information concerning any possible changes.

General function of the committee. The committee reviews and evaluates data on the safety and effectiveness of marketed and investigational human drugs for use in endocrine and metabolic disorders.

Agenda—Open public hearing. Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Those desiring to make formal presentations should notify the contact person before May 9, 1997, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time required to make their comments.

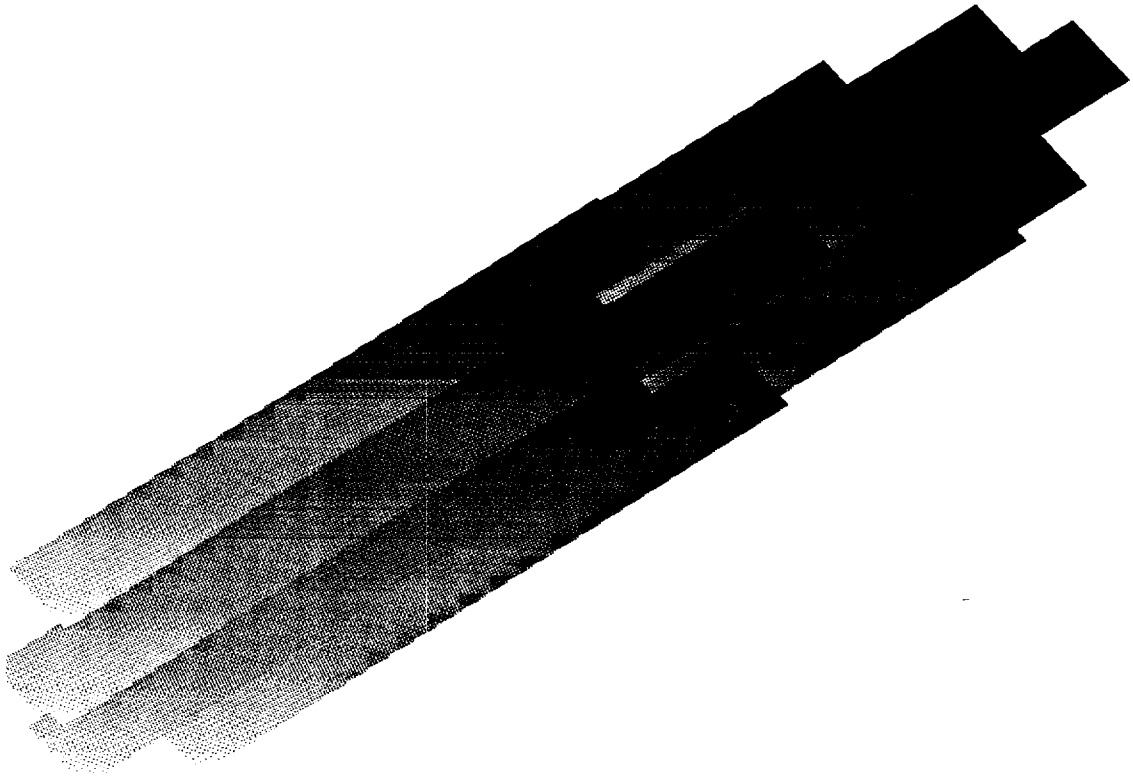
Open committee discussion. The committee will hear presentations and discuss data submitted regarding new drug application 20-766, Xenical™ (orlistat, tetrahydrolipstatin, Hoffman-LaRoche, Inc.) for long-term treatment of obesity.

FDA public advisory committee meetings may have as many as four separable portions: (1) An open public hearing, (2) an open committee discussion, (3) a closed presentation of data, and (4) a closed committee deliberation. Every advisory committee meeting shall have an open public hearing portion. Whether or not it also includes any of the other three portions will depend upon the specific meeting involved. There are no closed portions for the meetings announced in this notice. The dates and times reserved for the open portions of each committee meeting are listed above.

The open public hearing portion of the meeting(s) shall be at least 1 hour long unless public participation does not last that long. It is emphasized,

Guidance for Industry

Current Good Manufacturing Practices For Positron Emission Tomographic (PET) Drug Products



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 1997

CP 1

Guidance for Industry

Current Good Manufacturing Practices For Positron Emission Tomographic (PET) Drug Products

Additional Copies are available from:

The Drug Information Branch
Division of Communications Management, CDER, FDA, HFD-210
5600 Fishers Lane, Rockville MD 20857
(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 1997

CP 1

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GUIDANCE FOR INDUSTRY[1]

CURRENT GOOD MANUFACTURING PRACTICES FOR POSITRON EMISSION TOMOGRAPHIC (PET) DRUG PRODUCTS

I. INTRODUCTION

This guidance document provides information on certain practices, procedures, and facilities used to manufacture positron emission tomographic (PET) radiopharmaceutical drug products. The primary focus is on current good manufacturing practice (CGMP) requirements that may cause particular concern due to the special characteristics inherent in the production and control of PET radiopharmaceutical drug products.

It is essential that all drug manufacturing comply with CGMP regulations for finished pharmaceuticals [21 CFR Parts 210 and 211]. Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) deems a drug to be adulterated if the methods used in, or the facilities or controls used for, its manufacturing, processing, packing, or holding do not conform to, or are not operated or administered in conformity with current good manufacturing practice to ensure that such drug meets the requirements of the Act as to safety, has the identity and strength, and meets the quality and purity characteristics it purports or is represented to possess.

This guidance describes some of the manufacturing operations and controls used to prepare PET radiopharmaceutical drug products. Compared with conventional drug product manufacture, the manufacture of PET radiopharmaceutical drug products presents unique regulatory concerns including, but not limited to the following:

- The short physical half-life of positron emitting radionuclides. Generally, no more than two or three half-lives should elapse between the end of radionuclide production and the completion of drug manufacture.

- The scale of manufacturing that typically parallels the demand of a relatively small

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[1]This guidance has been prepared by the Office of Compliance (HFD-300) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the manufacture of positron emission tomographic (PET) radiopharmaceutical drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

number of patients. Manufacturing may be limited to only one or a few lots produced each day with a lot being as small as one vial.

- The need to administer PET radiopharmaceutical drug products to patients within a short period of time after manufacturing because of the short physical half-lives of these products.

FDA has proposed amending its regulations to permit manufacturers of PET radiopharmaceutical drug products to petition FDA for exceptions or alternatives to provisions of the CGMP regulations (60 FR 10517). FDA expects to finalize the amended regulations soon. Under the revised regulations, FDA may approve a request for an exception or alternative that meets certain requirements. FDA's actions are intended to relieve manufacturers of PET radiopharmaceutical drug products from regulations that (1) might result in unsafe handling of these products, (2) are inapplicable or inappropriate, and (3) do not enhance safety or quality in the manufacture of PET radiopharmaceutical drug products. The Agency may approve a request for an exception or alternative if: (1) The requestor's compliance with the CGMP requirement is unnecessary to ensure that the drug meets the safety requirements of the act and has the identity, strength, quality, and purity characteristics it purports to possess; (2) compliance with the requirement cannot be achieved; (3) the requestor's alternative procedures or controls satisfy the purpose of the requirement; or (4) the requestor's submission otherwise justifies an exception or alternative.

To maintain a publicly available record of requests for exceptions and alternatives and Agency action on such requests, FDA has decided that requests for exceptions and alternatives should be submitted in the form of a citizen petition under 21 CFR 10.30. A request for an exception or alternative should be clearly identified as a PET Request for Exception or Alternative to the CGMP Regulations. A citizen petition requesting an exception or alternative should contain one or more of the following: (1) An explanation, with supporting data as necessary, of why compliance with a particular requirement of the CGMP regulations is unnecessary or cannot be achieved; (2) a description, with supporting data as necessary, of alternate procedures or controls that satisfy the purpose of the CGMP requirement; or (3) other information justifying an exception or alternative. These three options will provide PET manufacturers the opportunity to present a variety of data and other information to support an exception or alternative.

This guidance does not attempt to address all sections of the CGMP regulations that might apply to PET radiopharmaceuticals. Radiation safety requirements and dispensing or administration of patient doses are not covered in this guidance. This guidance does not in any way affect the ability of the Agency to establish specific requirements or standards regarding PET radiopharmaceutical drug products within the context of new drug application reviews. Likewise, this document is not intended to address specific issues related to such applications.

This guidance supersedes the "Guide to Inspections of Liquid Injectable Radiopharmaceuticals

Used in Positron Emission Tomography (PET)," November 1993.

II. QUALITY CONTROL UNIT

A. Regulatory Requirements

A *quality control unit* is any person or an organizational element designated by the firm to be responsible for the duties related to quality control [21 CFR 210.3(b)(15)]. The quality control unit has responsibility and authority for certain actions [21 CFR 211.22]:

1. Approving or rejecting components, containers, and closures [21 CFR 211.84], in-process materials [21 CFR 211.110], and quarantined finished products [21 CFR 211.142 and 211.165].

2. Reviewing and approving or rejecting written documents and records, such as production and control procedures and specifications [21 CFR 211.100], and production and control records [21 CFR 211.192], ensuring that no manufacturing deviations (errors) have occurred.

3. Fully investigating manufacturing deviations, if they occur [21 CFR 211.192].

4. Maintaining complaint files involving the possible failure to meet predetermined drug product specifications [21 CFR 211.198].

B. Guidance

Some quality control units in some PET centers may consist of just a single person, provided the center's workload is sufficiently low to justify such staffing levels. In other situations, employees who are not directly related to PET production and who are fully trained and qualified may perform functions in the quality control unit.

In some limited, justified situations, individuals may be simultaneously responsible for both quality control and production functions. Outside consultants with appropriate qualifications may perform one or more of the functions of the quality control unit [21 CFR 211.34]. Where a single person is ultimately responsible for both the quality control unit and production, an outside consultant should perform at least some of the quality control unit functions. Such delegated functions could include the review and approval of written documents, procedures, and specifications.

Regardless of the staffing levels or pattern of personnel assignment, the quality control

unit should have the necessary authority to ensure that the functions of the unit are both fully and objectively achieved. The unit's authority and responsibility should not be subordinated to any other unit. The unit should maintain autonomy in rendering and implementing the decisions necessary to ensure adequate process control and the quality of released products. For example, once decisions are made by the quality control unit to reject lots, such decisions should not be subject to further review or revocation by another organizational component or person. Written procedures should be established to ensure that the responsibilities listed above are fulfilled.

III. PERSONNEL QUALIFICATIONS

A. Regulatory Requirements

Appropriate and adequate training of personnel is required in 21 CFR 211.25. According to the regulation, a staff member must have the education, training, and experience, or combination thereof, to enable that person to perform his or her assigned functions. The regulation also requires that supervisors have appropriate knowledge and skills.

B. Guidance

FDA acknowledges that some PET centers may be operating with as few as one or two people to accomplish all production and control functions. Nevertheless, production and control personnel in all PET centers should have a broad range and level of appropriate formal education, training, and experience in the areas of radiopharmacy, radiochemistry, nuclear physics, manufacturing and testing of PET radiopharmaceuticals, as well as current good manufacturing practices.

All personnel performing aseptic processes should be thoroughly trained in these techniques and in maintaining aseptic environmental quality. This training should be in addition to that necessary to properly manufacture PET radiopharmaceutical drug products. All training should be appropriate to the scale and configuration of the aseptic operation in which personnel are working.

One example is the general principle of keeping gloved hands away from critical areas and surfaces while preserving the laminar airflow. Generally, different manipulative approaches are used depending upon whether the operation is manual or automated and whether it is performed under vertical or horizontal flow. All personnel entering a controlled area should be appropriately trained in procedures (e.g., gowning) used for maintaining adequate environmental controls in the PET center.

Because the maintenance of environmental quality and the prevention of product

contamination are heavily dependent upon adequate personnel practices within all controlled environments, personnel practices should be monitored. At established intervals, an experienced, knowledgable observer should objectively assess the aseptic technique and environmental control practices of all personnel. These evaluations also should include routine physical assessments of aseptic technique and environmental control practices, such as swab or touch plates testing. Personnel employing unapproved practices should be retrained and requalified before resuming procedures in the critical areas or before reentry into the controlled area is permitted.

FDA does not expect most PET centers with small staffs of scientific and professional personnel to have in-house training programs. However, all PET centers should have an appropriate, written plan that is followed closely to ensure that each staff member maintains current, necessary professional-scientific competency, including competency in current good manufacturing practices. This written plan may include programs from externally provided continuing education, training, or directed experience (in-house training programs).

IV. BUILDINGS, FACILITIES, AND PERSONNEL RESPONSIBILITIES

A. Regulatory Requirements

21 CFR 211.42 (design and construction) requires separate or defined areas of operation to prevent contamination and, in conjunction with aseptic processing, high-efficiency particulate air (HEPA) filtration, positive pressure, proper equipment maintenance to control aseptic conditions, and a system for monitoring environmental conditions.

21 CFR 211.46 (ventilation, air filtration, air heating and cooling) requires, in part, that equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature be provided where appropriate and that an air filtration system, including prefilters and high efficiency particulate air (HEPA) filters, be used when appropriate on air supplies to production areas.

21 CFR 211.28(a) requires that protective apparel be worn as necessary to protect drug products from contamination. 21 CFR 211.28(d) requires a person having any illness or open lesions that may adversely affect the safety or quality of drug products be excluded from direct production activities.

21 CFR 211.56 (sanitation) requires, in part, written procedures for clean and sanitary conditions in any building used for manufacture of drug products.

B. Facility Design and Function

The facility design for that part of the PET center where radiopharmaceutical drug products are manufactured should protect the product from possible contamination from personnel, equipment, and the surrounding environment.

NOTE: Facility design also should protect personnel from unnecessary radiation exposures and hazards. The principles of radiation protection and safety are not included as part of this CGMP guidance. Other regulatory guidance and sources should be consulted regarding this subject.

Environmental conditions can significantly contribute to potential microbial and particulate contamination of aseptically processed products. *Critical areas* are those in which the sterilized dosage forms, containers, and closures are exposed to the environment, particularly the environment immediately surrounding aseptic-processing activities and critical surfaces (a *critical surface* is any surface that comes into contact with a sterilized product, sterile containers, or sterile closures). FDA's "Guideline on Sterile Drug Products Produced by Aseptic Processing" (June 1987) provides further guidance on critical and controlled areas.

Strict control of the microbial and particulate loads in the critical areas and around critical surfaces is essential. PET centers should consistently maintain at least Class 100 conditions in the atmosphere immediately surrounding critical areas and surfaces during aseptic activities.

The microbial and particulate characteristics within the controlled area (Class 100,000) and within the buffering conditions (preferably maintained at Class 10,000) have direct effects on a PET center's ability to maintain the appropriate conditions in areas immediately surrounding critical areas and surfaces. It is essential to prevent microbial and particulate contamination of the manufacturing process and the final product.

All activities performed under aseptic techniques involving critical surfaces should be performed in critical areas that are maintained under at least Class 100 conditions. Critical activities in the manufacture of PET radiopharmaceuticals may include, but are not limited to:

1. Aseptic addition of a sterile diluent, such as sodium chloride 0.9% injection, to a sterile, stoppered vial using needle/syringe technique

2. Aseptic attachments of sterile components and devices

Examples of such activities include: connection of a sterile syringe or a sterile filter device to a sterile needle; insertion of a sterile needle through a sanitized

stopper into a vial; and any penetration of, or creation of an open pathway into a sealed container-closure system after filling, as might occur with some postfilling sampling techniques.

NOTE: If activities 1 and/or 2 are performed improperly, there is a potential for contamination of the sterile product or sterile product contact surface.

3. Allocation of a lot of an injectable PET radiopharmaceutical into unit-dose containers

To ensure that activities, such as aseptic tasks, are maintained within the designated criteria for critical areas and for critical surfaces, the Class 100 areas should be completely surrounded by buffering conditions, preferably maintained at least at Class 10,000 conditions. The buffering conditions, in turn, should be located within a controlled area maintained at least at Class 100,000 conditions.

C. Critical Areas and Surfaces (Class 100); Buffering Conditions (preferably Class 10,000)

As defined above, a critical area is one in which the sterilized dosage form, containers, and closures are exposed to the environment. Activities conducted in critical areas include any manipulations of sterilized materials or products prior to and during the filling or closing operations. These activities are conducted in what is typically known as the aseptic core or aseptic processing area.

A critical area (Class 100) is essential because the finished product is not processed further in its immediate container and is vulnerable to contamination. Therefore, to maintain the quality and, specifically, the sterility of the product, the environment in the immediate proximity of the actual operations should be of the highest quality.

One essential aspect of environmental quality is the particulate content of the air. Particles can enter a product and contaminate it physically or biologically by acting as a vehicle for microorganisms. It is important to minimize the particle content of the air and to effectively remove those particles that are present. Maintaining a minimum of Class 100,000 in the controlled area with buffering conditions, preferably at Class 10,000 conditions, provides an acceptably low risk of contaminants being blown, dragged, or otherwise introduced into the critical areas and critical surfaces from the surrounding atmosphere. Critical areas and critical surfaces should be fully enveloped with buffering conditions (preferably maintained at least at Class 10,000 conditions).

One potentially significant source of microbial and particulate contamination is room air. Air in critical areas should be supplied as HEPA filtered laminar flow air, having a velocity sufficient to sweep particulate matter away from the filling and closing area.

Normally, a velocity of 90 feet per minute, plus or minus 20 percent, is adequate. However, higher velocities may be needed where operations generate high levels of particles or where equipment configurations disrupt laminar flow. Measurements should be taken at the HEPA filter face and at the product filling heights to determine acceptability. Microbial contamination not exceeding one colony forming unit per 10 cubic feet is considered attainable and desirable.

Different areas in the manufacturing process should be separated by absolute physical barriers (e.g., solid panels) whenever possible and may be supplemented as necessary by partial physical barriers (e.g., air curtains) and procedural controls. In addition, the recommended use of minimum Class 100,000 controlled areas with buffering conditions (preferably at least Class 10,000) should be adequate to achieve and maintain conditions for performance of aseptic techniques within the designated Class 100 critical areas.

In meeting the requirements of 21 CFR 211.42, PET centers can perform aseptic techniques within suitable, effective critical areas located in a vertical or horizontal laminar airflow workbench (LAFW). Aseptic techniques within an LAFW may include relatively simple manipulations of commercially available, sterile, ready-to-use sealed devices, tubing and containers.

In using a vertical or horizontal LAFW, an acceptable separation between areas within the manufacturing facility could be achieved as follows:

1. Separating buffering conditions from the controlled area

    a. With vertical recirculating LAFWs

    The front panel is lowered to manufacturer specifications. A constant air barrier is provided below the panel, and the proper technique is used for the introduction of articles into the buffering conditions.

    b. With horizontal LAFWs (no front panel)

    Maintaining Class 100 conditions within the critical area is entirely dependent on the outflow of air moving horizontally across the critical area. Therefore, the entire opening to the critical area should be protected from gusts of air entering the buffering conditions from the controlled area. One solution could be to hang plastic sheeting in such a manner as to create an acceptable buffering condition surrounding the front of the horizontal LAFW's opening, effectively isolating the critical area from the controlled area. This plastic sheeting should extend several feet above the top of the LAFW work space, surround all three sides, and extend at least 12 inches below the level of the critical area.

Overlapping panels of plastic sheeting, which would allow ready entry and exit of personnel and goods, may be acceptable.

The appropriate distance between the edge of the critical area and the back plastic panel should be determined and established to maintained an adequate air flow. The distance should be adequate to ensure and prevent deviations in the rate of laminar air flow near the edge of the critical area. The proper distance should be confirmed by the combination of visual evaluation of air flow patterns (e.g., with vaporizing dry ice) and airflow velocity measurements.

2. Separating buffering condition from the critical area inside an LAFW

Within the LAFW, a specific section should be designated and demarcated as the critical area within which only critical activities, such as aseptic processes, are performed. The front boundary of this area should be at least six inches from the front edge of the LAFW. The side boundaries should be appropriately placed relative to the number of critical and noncritical functions to be performed inside the LAFW, and the number of articles being used for these tasks. Boundaries should be clearly recognizable, for example, by observable markings.

In vertical LAFWs, tasks and articles involved in aseptic processing should be properly positioned within the demarcated critical area. Some facilities have ensured proper positioning by establishing a perforated platform within the critical area.

In horizontal LAFWs, operations involving aseptic processing should be carried out as close to the airflow source as possible. Operators should wear face masks for breath deflection. Appropriate spatial arrangement of objects and procedures should ensure that the physical or conceptual interface separating the Class 100 area and the buffering conditions is constantly maintained.

The clean air envelope is established by the HEPA-filtered, laminar flowing air in the critical area. A continuous flow of unobstructed air is essential when performing aseptic tasks. Written procedures should be established and followed by operators performing aseptic tasks in the critical area to ensure the clean air envelope is maintained. Room air may not be the only gas in close proximity to the critical area and aseptic operations. Other gases, such as nitrogen or carbon dioxide, which may contact the product, container or closure, or product surfaces (e.g., purging or overlaying) should be appropriately sterile filtered to maintain high particulate and microbial quality. In addition, compressed air should be free from demonstrable oil vapors.

Critical areas should have a positive pressure differential relative to adjacent controlled areas. A pressure differential of 0.05 inches of water is acceptable. Aseptic processing should always be performed in critical areas under a positive airflow pressure. The adjacent controlled area and the rest of the building may have negative airflow pressures. One method for achieving these airflow gradients is to use airlocks or an anteroom between the aseptic processing areas and the rest of the building.

Final container assembly should be performed to totally close the system prior to its removal from the critical area. For example, the steps in such a closed process might include:

a. Connecting a 0.2 μm sterilizing filter to the fluid pathway needle in the final container

b. Attaching a 0.2 μm filter as the vial's air vent needle, if needed

c. Affixing a 0.2 μm filter or a new sterile syringe to a pre-attached sampling port needle

Precautions should be taken to prevent slippage or detachment of components in the aseptically closed final container assemblies from the chemical synthesis apparatus.

The following steps are not considered to be aseptic processes and do not need to be conducted in the critical area:

a. Attaching the distal tubing from the synthesis apparatus to the upstream connector of the sterilizing filter

b. Drawing the postfilling sample from the vial through the filtered sampling port

c. The rapid removal of a needle from the stopper after filling

However, when sampling for sterility testing involves the withdrawal of a drug product from a filled vial, the procedure **should** be performed as an aseptic process in suitably controlled environmental conditions to protect the test sample from potential microbial contamination. (See Sampling in Section X.)

D. Controlled Area (Class 100,000)

The LAFW should be located in a controlled area. Many PET centers can successfully

achieve acceptable air quality in the controlled area without special air handling controls. Air in controlled areas is generally of acceptable particulate quality if it has a per-cubic-foot particle count of not more than 100,000 in the size range of 0.5 micron or larger (Class 100,000) and a microbial count not exceeding 25 colony forming units per 10 cubic feet.

Certain fundamental precautions should be provided and observed to ensure that air quality is acceptable:

1. The LAFW should be situated in the section of the room with the least amount of traffic and activity, preferably at the end opposite the doorway.

2. Aseptic processing tasks should be performed during defined time periods. Ideally, they should be performed when there is a low potential for particulate and bacterial contamination (i.e., during a continuous period of little or no activity within the adjacent controlled area.) Consideration might be given to the preparation of container assemblies at the beginning of the day before other daily activities begin and before additional personnel have entered the room.

3. Surfaces within critical and controlled areas should be constructed of smooth, easily cleanable, nonshedding materials. The controlled area should not be carpeted, or have porous floors, walls or ceiling tiles that cannot be properly cleaned or sanitized. The controlled area also should be free of overhanging pipes or fixtures.

4. All parts of the controlled area should be easily accessible for cleaning and disinfecting. Equipment and furniture used in the controlled area should be constructed of smooth, cleanable, nonshedding materials whenever possible. According to the PET center's written policies and procedures, cleaning and disinfecting surfaces, equipment, and furniture should be accomplished using standard approaches to good housekeeping.

5. The surfaces in all areas should be cleaned and sanitized with suitable frequency by specially trained personnel. Written policies and procedures for cleaning and sanitizing surfaces, equipment, and furniture should be designed to ensure consistent achievement of the intended or specified microbial and particulate quality for that area.

The degree of microbial and particulate control in the controlled area may be less stringent than that for the buffering conditions or the critical areas. However, the extent of cleaning and sanitizing should ensure that the barrier capabilities between the buffering condition and the controlled area are not over

challenged.

6. Activities and functions that are not absolutely necessary or part of the actual processing of PET radiopharmaceutical drug products should not be performed in the controlled area. Unnecessary personnel traffic should be minimized. Particulate-generating activities, such as removal of solutions, drugs, chemicals, and supplies from cardboard boxes should not be performed in the controlled area. Likewise, office supplies and reference books should not be permitted in the controlled area.

In considering what equipment should be located in or what tasks should be performed in the controlled area, an optimal balance between functional necessity versus the contribution as potential sources of contamination should be an essential part of the decision-making process.

7. Personnel entering the various areas or performing particular tasks should wear appropriate protective apparel and follow procedures that are appropriate for the level of cleanliness required for a specific area. Personnel should wear clean clothing covers or clean long-sleeved lab coats that generate low numbers of particles (e.g., material such as Tyvek). Head and facial hair should be covered, and shoe covers worn in the controlled area. Clear gowns or closed coats with sleeves should have elastic bindings at the cuffs. The wearing of jewelry on the hands, fingers, and around the wrist should be minimized or prohibited.

8. The number of personnel in the controlled area at any time should be limited as another measure to promote general cleanliness. Eating, drinking, smoking, and wearing or applying cosmetics should never be permitted in the controlled area.

9. When working in an LAFW cabinet, sterile gloves should be used with cuffs that extend over the lab coat sleeves. Aseptic techniques should be consistently employed. For example, articles should be kept as deep as possible within both the buffering condition and the critical areas. Face masks should always be worn during the performance of aseptic procedures.

10. Written policies and procedures should be established and followed that are appropriate for the intended level of cleanliness of the areas. A specific concern is the proper introduction of articles from one area to an area of higher quality. Only clean, low-shedding or nonshedding articles may be introduced into the buffering condition. The surfaces of non-sterile items should be sanitized with an appropriate disinfectant (e.g., sterile 70% isopropyl alcohol) before being placed in the critical area. Only sanitized or sterile articles

introduced from the buffering condition should be placed in critical areas.

E. Cleaning and Disinfection

General custodial personnel from the medical center or equivalent should be able to perform some cleaning and sanitizing functions for the controlled area. When housekeeping personnel are involved in cleaning the controlled area, they should receive adequate training, follow applicable procedures, and be supervised by trained PET center personnel.

The cleaning, sanitizing, and organizing of the critical area and buffering condition should be the responsibility of trained and supervised PET center personnel who follow appropriate written policies and procedures. Cleaning, sanitizing, and organizing the critical area and the buffering condition should be performed at least twice (i.e., before and after) for each distinct operation or procedure.

Before each distinct operation or procedure, all items should be removed from the critical area. All surfaces of the criteria area should be wiped clean with a freshly prepared mild detergent followed by an approved sanitizing agent. Personnel should allow sufficient time for the sanitizing agent to achieve its antimicrobial effect.

Recleaning should be performed during operations if spillage or other events indicate such a need. It should be realized, however, that recleaning activities may disrupt the atmosphere surrounding the critical area and present a potential for product contamination.

Work surfaces and counter tops near LAFWs in the controlled area should be cleaned in a similar manner. Storage shelving in the controlled area should be emptied of all supplies and then cleaned and sanitized using approved agents with effective frequency. All articles should be cleaned before reshelving.

Cleaning and sanitizing should be sufficiently frequent to ensure the consistent control of environmental quality, as determined through the routine collection of environmental monitoring data. One should not wait until environmental data show that the facility is going or has gone out of control before initiating cleaning or sanitization. See the section on Environmental Monitoring below for further information.

Supplies, equipment, and other articles introduced or brought into the buffering conditions from the controlled area should be wiped with a suitable cleaning agent or removed from their shelf-storage cartons or containers at the interface between the controlled area and the buffering conditions. Subsequently, nonsterile articles should be sanitized with a suitable disinfectant. Sterile articles should be removed from their protective package or wrap (taking care not to open sterile fluid pathways or expose

sterile product contact surfaces) at the interface between the buffering conditions and the critical area.

Cleaning and sanitizing activity in an LAFW should proceed in a direction away from the critical area. Cleaning of the controlled area should begin at the end of the buffering conditions, and proceed in all directions away from the buffering and critical areas. Storage shelving should be emptied of all supplies when cleaned and sanitized, and articles should be cleaned before reshelving. Cleaning and sanitizing should be scheduled and performed by trained and supervised personnel according to written policies and procedures using validated methods.

Only approved cleaning and sanitizing agents should be used. Sanitizing agents should be effective against bacterial spores and a wide variety of microorganisms that are likely to be encountered on the work surfaces. Seventy percent isopropyl or ethyl alcohol that has been filtration sterilized and is checked periodically for evidence of visible contamination can be used. However, seventy percent isopropyl or ethyl alcohols are not the only sanitizing agents that may be used for these purposes. Cleaning and sanitizing agents should be compatible with their surfaces and should not leave unacceptable chemical residues or films.

Wipes should be disposable. All reusable cleaning articles such as sponges and mops should be dedicated for their specific area of use (i.e., inside the critical area (LAFW) or for the controlled area). Wipes and sponges used inside the critical area (LAFW) should be made of nonshedding material. Cleaning materials (e.g., sponges, mops, wipes) used in the controlled area should be constructed of low shedding material. Reusable cleaning materials (such as mops and sponges) should be properly cleaned, rinsed, and, where indicated, sterilized prior to their reuse according to written policies and procedures using validated methods.

F. Equipment Testing

The routine and regular integrity testing of the LAFWs HEPA filters is essential to ensure that the environmental quality of the critical area is maintained. Integrity testing of HEPA filters (e.g., DOP challenge tests) is used to detect leaks around the sealing gaskets, through frames, or through the filter medium. Certification of the LAFW should be performed by a qualified contractor when the unit is initially installed, if it is moved and at suitable intervals, typically every six months. More frequent testing may be necessary when air quality is found to be unacceptable, as part of an investigation into a finding of nonsterility in a drug product, or when significant leakage or other defects are detected at the 6-month interval. The prefilters in the LAFW should be changed periodically according to written policies and procedures by qualified PET center personnel.

The laminar airflow velocities should be monitored regularly at the work surface as well as at the HEPA filter face to ensure adequate uniformity throughout the critical area. Equipment problems can alter airflow velocity. Significant imbalances or reductions in airflow velocity can occur that alter or even extinguish the laminar flow of air to an extent that adequate protection of the critical area is lost. The operator may not be aware of such malfunctions or inadequate conditions. Because the instrumentation and techniques for monitoring airflow velocity are relatively inexpensive, simple, and quick, at least monthly checks of airflow velocity by PET center personnel are highly recommended.

It is essential to maintain appropriate air quality and flow, which can be easily disrupted or influenced by structure, objects, and configuration of equipment and articles within the critical area. Disruptions or influences on air quality and flow can cause undesirable stagnant air pockets, eddy currents, and backwash of potentially contaminated air into the critical area. These disruptions or influences on airflow should be evaluated by assessing to ensure that Class 100 conditions are maintained.

One simple and acceptable approach for observing airflow patterns uses visible carbon dioxide vapors from dry ice placed in the proximal airstream. The visible CO_2 stream can demonstrate influences on or disruptions in airflow around objects and past surfaces. An acceptable configuration for airflow within the critical area should help ensure that Class 100 conditions are maintained. Established configurations of equipment and operations should be followed. If changes occur in equipment configuration, operations, or workflow, reevaluation of airflow patterns within the critical area should be performed.

G. Environmental Monitoring

The classification of controlled environments is based upon the measurement of total nonviable particle counts (see the Federal Standard 209E Clean Room and Work Station Requirements for controlled environments). Particulate monitoring should be performed at least daily under dynamic conditions in the presence of actual production equipment with the configuration of personnel present and during actual production activities. It is essential to ensure that Class 100 conditions are being maintained in the critical area, and that the buffering conditions are maintained, preferably at least at Class 10,000 conditions.

Particulate monitoring is usually performed with electronic instruments displaying immediate results that relate particle size and counts, volume of air, and sampling time and duration. Different types of instruments are available. Measurements can be made as needed, or, with most instruments, automatically obtained on a planned, ongoing schedule. Instantaneous availability of results permits real-time assessment of environmental particulates and permits rapid adjustments in the control program. It

should be noted, however, that particulate monitoring does not distinguish between viable and nonviable particulates.

In aseptic processing, one of the most important controls is the establishment of an appropriate environmental monitoring program. The facility should be monitored in a manner adequate to demonstrate that the intended environmental conditions are consistently maintained and to warn when environmental quality is going or has gone out of control. An environmental monitoring program for PET centers should include, at a minimum, the microbial sampling of surfaces and personnel, the monitoring of observable personnel performance during the manufacturing process and when performing aseptic techniques, and the monitoring of the facility's overall environmental control policies and procedures.

Surface monitoring procedures should be adequate to ensure consistent, effective disinfection and to ensure compliance with proper techniques to avoid recontamination. Daily or lot-by-lot surface sampling in the critical area and the buffering conditions should be performed. Contact (e.g., Rodac) plates or swab-rinse techniques are usually acceptable methods. However, the appropriateness and acceptability of these methods will depend upon the location and intended use of the surface sampled.

Contact plates should not be used on surfaces where complete removal of any residual agar cannot be fully ensured. Fluids used for the swab rinse procedure should not inhibit microbial growth. A combination of sampling sites and scheduling of samples should be representative of the greatest number and the widest range of microorganisms that are most likely to accumulate in the facility.

Written procedures should ensure that personnel are continuously monitored throughout the manufacturing process to ensure that proper gloving, gowning, glove sanitization, and touch control techniques are performed. A standard touch-plate method can be used by pressing the forefinger tips and thumb tips of the gloved hands against an agar surface using a consistent firmness.

As part of an operator's initial gloving qualification, touch-plate fingertip testing should be performed and certified free of microbes at the conclusion of the gloving procedure. After initial qualification, daily postprocessing fingertip, touch-plate testing should be performed during routine production operations. This type of daily testing should be continued until the operator's use of proper techniques has been established as evidenced by consistently low fingertip contamination. All qualification and testing methods should be established in and performed according to the PET center's written policies and procedures.

It should be noted that the complete absence of microorganisms on fingertips is not a realistic expectation during routine production. Operators are handling sanitized but

not sterilized surfaces during their aseptic manipulations.

Microbial monitoring has its greatest value when recoveries show trends (consistent or otherwise) or acute out-of-limit observations. The monitoring data should be regularly reviewed as part of the current critical evaluation. When any abnormal trends or out-of-limit observations occur, an investigation should be conducted promptly and should include the following:

1. Identify (by at least genus) the organism in a positive sterility test
2. Review the laboratory's record of tests over time
3. Monitor production area environments
4. Determine the product's presterilization bioburden
5. Review batch production records

Some possible causes for abnormal trends can include:

1. Established or developing unacceptable environmental conditions
2. Poor personnel practices
3. Microbial resistance to disinfectants
4. Inadequate cleaning and disinfectant schedules

At a minimum, PET centers should have an aseptic technique monitoring program for personnel. All operators who perform aseptic manipulations under laminar airflow should accomplish these techniques in a proper and consistent manner, as described in the PET center's written procedures. For example, an evaluation of operator performance of aseptic technique should highlight: (1) Avoiding touch contamination and blockage between the source of the laminar airflow and the critical area; (2) disinfection of areas and work preparation; (3) arrangement of supplies in the work areas and work flow; and (4) sanitization of gloves and articles to be introduced into the buffering conditions and the critical area. The performance of each operator should be repeatedly and objectively evaluated at meaningful time intervals.

Personnel should be trained to detect and correct procedural flaws that might develop. The key is to have a training and evaluation program that prevents, rather than corrects, entrenched problems. Supervisory personnel should be capable of performing objective

evaluations of aseptic techniques based on direct observations and their knowledge of the proper aseptic techniques.

Environmental monitoring also includes evaluating air quality. The literature documents many instances of product contamination caused by bacterial aerosols. Contaminated products have led to outbreaks of bacterial-associated illness and, in some instances, human disability or death. Contamination may also introduce allergens and pyrogens, reduce drug potency, or promote the formation of toxic substances. Such changes could result in the recall, reprocessing, or destruction of the finished pharmaceutical.

Various types of air samplers are available for monitoring the environment and may include liquid impingers, agar impactors, filtration, settling plates, centrifugation, and electrostatic and thermal precipitators. The selection of a sampler or combination of these depends on the special needs of the user, but should contain both active as well as passive sampling techniques. At a minimum, air sampling should occur at least once during each manufacturing cycle. Ideally, air sampling to measure environmental air quality should be performed before the production cycle begins, on initiation, in the middle, and at the end of the manufacturing process.

A written environmental monitoring program should have a scientifically sound sampling schedule, including sampling locations and frequency. In addition, maximum microbial limits should be established along with a definitive course of action to be taken in the event samples are found to exceed established limits. In general, these specified limits should represent conservative values intended to signal potential or actual drifts from the designated levels of quality. These specific limits are commonly referred to as *alert* and *action* limits. In the written environmental monitoring program, there should be an appropriate plan of action that will be initiated whenever the alert and action limits are exceeded.

H. Building Cleanliness and Sanitation

Some PET centers are located in hospitals or medical centers where routine housekeeping for the building proper would be expected to ensure a level of general cleanliness and sanitation suitable for patient care and clinical functions. Such standards are generally adequate to insure cleanliness for the non-controlled areas.

When institutional personnel normally not assigned to the PET center are involved in the cleaning or maintenance within the controlled area, they should receive adequate training on applicable procedures and be supervised by trained PET personnel.

V. EQUIPMENT

A. Regulatory Requirements

21 CFR 211.65 requires, in part, that equipment be constructed so that surfaces that contact components, in-process materials, or drug products are not reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

21 CFR 211.67 requires, in part, that equipment be cleaned, maintained, and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond its established requirements.

21 CFR 211.68 requires, in part, that automatic, mechanical, electronic, or computer equipment be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance.

B. Target Container and Tubing System

All PET centers should demonstrate and document that the entire manufacturing process used to produce a PET radiopharmaceutical drug product does not alter the product or render it unsuitable for use as the result of contacts with fluid pathways, inner surfaces of vessels, or other product contact surfaces used in the manufacturing processes. PET centers should have data demonstrating the suitability of their manufacturing processes readily available for review and inspectional purposes.

For example, a PET center should be able to document that the particle bombardment process produces an appropriate and consistent effect on the target material. Consideration should be given to any alternation or impurity that might result from target bombardment such as pitting or leaching of the target. Data should document that no such alternations or impurities occur that might adversely affect the target material or the desired radioactive postbombardment substance (radionuclide).

Tubing, valves, chambers, columns, and other related attachments may comprise the various fluid pathways, reaction chambers, portals, etc. in manufacturing processes. All materials used for the entire manufacturing process, including the chemical synthesis (from the particle accelerator-target bombardment to final filtration) should be compatible with the in-process materials and the desired PET radiopharmaceutical drug produced. These materials should not absorb in-process materials, and not leach unintended substances into in-process materials or the finished drug product.

The PET center should have evidence (data) available documenting the compatibilities of all systems and should be knowledgeable of these systems to ensure that only

compatible materials and components are being used in each manufacturing process. Material and component compatibility may also be demonstrated and documented by means other than in-house testing where appropriate.

PET centers should also have adequate documentation available (data) to ensure that all equipment and systems are suitable for their entire duration of use and for the maximum number of lots for which they will be used before replacement. Consideration should be directed to, but not limited to factors such as physical-chemical compatibility, adsorption, leaching, integrity, bioburdens, and pyrogen control. Effects such as aging (stress cracking and brittleness) and the radiation effects on polymer materials should also be included as part of the documented evaluation of materials-systems compatibility.

C. Pyrogen (Endotoxin) Control

The introduction and growth of pyrogen-generating microorganisms within the system should be prevented during the entire manufacturing process. To achieve this, the system should be pyrogen free at the outset. The tubing system should not become a pyrogen source. Daily or lot-by-lot replacement of pyrogen-free tubing is recommended whenever feasible. Where not feasible, a closed system should be maintained that ensures the system is dry during substantial downtime periods.

A closed, dry system may be facilitated by flowing sterile filtered dry gas (air or nitrogen) through the system following the manufacture of a lot. The system can be closed by attaching bacterial filters or reservoirs (e.g., syringes) at each portal with daily replacement, or by limiting entries into the system through syringe-needle penetration of swabbed gum rubber ports. Any procedures requiring the opening of such a system (e.g., to connect transfer devices or other articles to an open portal) should be performed as quickly as possible. Such manipulations may be performed in the controlled area, providing the environmental conditions are suitably controlled.

There may be some systems or parts of the manufacturing system (purification cartridges or syringes of [^{18}O] enriched water) that cannot be dried or replaced on a lot-by-lot basis. In such cases, there should be validated procedures for daily sanitization as an acceptable alternative method to achieve adequate pyrogen control.

The duration of use and frequency of replacement for tubing and related manufacturing equipment should be validated to ensure adequate endotoxin control for the specified time period and under *worst case* operating conditions.

Some phases of the synthesis process may inherently destroy pyrogens. For example, the addition of a strong oxidizing reagent and the application of high heat in the synthesis of [^{18}F] FDG Injection has the potential for pyrogen destruction. It is

essential to document and to validate any step claiming to promote pyrogen destruction. The successful demonstration of a minimum three-log reduction to suitable endotoxin challenge usually constitutes acceptable evidence of adequate pyrogen destruction.

Predetermined action levels of endotoxin (i.e., lower than the specified release levels) should be established. When this action level is exceeded, prompt follow-up should include:

1. Replacement of all components in the manufacturing system before production of the next lot.

2. A thorough investigation of potential sources of pyrogens with correction action as necessary.

3. Appropriate reduction of the timing between replacement of manufacturing components until there is adequate evidence to ensure pyrogens are adequately controlled. If consistent endotoxin control cannot be demonstrated with extended-use components, then extended-use components should not be used in the manufacturing process.

FDA's "Guideline for Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices" (12/87) provides guidance on how to determine endotoxin limits. Endotoxin limits associated with the production of PET radiopharmaceuticals should be based on the assumption that the entire volume of an anticipated lot could potentially be administered to a single patient.

D. Particle Accelerator

The particle accelerator (a cyclotron or linear accelerator) is generally the initial component in the manufacturing process for PET radiopharmaceuticals. Several parameters define the appropriate operation of the particle accelerator. These operating parameters directly influence the potency, purity, quality, and characteristics of the radioactive postbombardment substance (radionuclide) produced for incorporation into the designated PET product.

The particle accelerator production methods and operating parameters should be adequately specified and appropriately validated. Written policies and procedures to document the function and the operation of the particle accelerator should ensure that all intended operating parameters will be followed. Most target materials, like [^{18}O] enriched water, are not generally manufactured in PET centers. Therefore, it is essential that the PET center verify the quality of the target materials.

For each lot of PET radiopharmaceuticals, the batch production and control records should document and verify that all operating parameters as specified in the master production and control records were followed. The limits for the operating parameters should not be exceeded as these parameters directly determine the quality and quantity of the radionuclide produced.

Parameters for the production of radionuclides may include, but are not limited to the following: maximum particle energy, beam current, threshold energy, energy of incident particles, duration of irradiation, proper alignment of the target, isotopic composition of target material, foil window composition ([^{48}V] impurity from irradiation on titanium foils), and the chemical purity of the target material.

PET centers should ensure that the functions and operations of instrumentation, apparatus, recording devices, and equipment that determine, affect, or measure all parameters are routinely calibrated, inspected, and checked. The schedule, extent of calibration, and inspection should be based on the equipment's installation, operational, and performance qualification characteristics. Specified functions and operations involving the particle accelerator or other equipment or instrumentation may be performed under service contracts. The schedule and calibration methods should be explained in the written procedures, and records should be available for inspection at the PET center.

FDA acknowledges that the particle accelerator's output may be adequate for the chemical synthesis of PET radiopharmaceuticals although its actual yield deviates appreciably from theoretical yields (see Section XIII). Some limited flexibility in particle accelerator-operating settings may be necessary to achieve clinically useful quantities of a finished drug product.

In some cases, certain production decisions may be made during the manufacturing of a lot of PET radiopharmaceutical (in the absence of specific written parameters detailing those decisions). When such ad hoc production decisions are made, they should be recorded and documented by designated personnel who are fully qualified by training and experience for certain technical judgments. Such changes should be documented and justified in the batch production and control record.

It is essential to ensure that only properly designated, fully qualified personnel control or make changes affecting the operation of the particle accelerator. Any computerized control programs governing the operation of the particle accelerator should have lockout capabilities within the software program. Effective physical lockouts to the computer controls or other appropriate mechanisms are also acceptable.

E. Synthesis

Synthesis encompasses the entire manufacturing process, consisting of numerous complex, interrelated steps including the addition of reagents, heating, drying, separation, rinsing, elution, chemical reaction, and related processes requiring close control. Generally, the synthesis process may be executed under automated or computer control.

Virtually every step in the manufacturing process is critical in that any deviation exceeding specified limits can potentially result in the finished PET radiopharmaceutical product failing to meet one or more of its quality specifications. The PET center's personnel are responsible for ensuring that the synthesis operation is capable of consistently and effectively meeting its predetermined specifications and that the manufacturing process is operated in a controlled manner.

The manufacturing process should be fully validated based on its operational specifications to produce a uniform product on a consistent basis without regard for an individual drug's release specifications. Validation ensures that all preestablished specifications for the drug's production are consistent with the specifications set out in the approved new drug application, drug master file, or master production and control record.

The entire manufacturing process should be preestablished and fully described in the master and batch production and control records. These records should identify the equipment and instrumentation that will be used in a specified and controlled manner as part of the approved synthesis process. Records should also ensure that all the necessary equipment is operational prior to the preparation of each lot. The daily manufacturing process should be a planned series of specified steps performed according to and verified in the written batch production and control records.

Equipment or instrumentation used in the manufacturing process may be subject to unanticipated problems or malfunction. PET centers should establish and maintain appropriate systems to monitor and to alert production personnel to malfunctions encountered during the drug manufacturing process. Should malfunctions occur, the cause(s) should be identified and any corrective interventions employed. PET centers should ensure that all operations and functions, instruments, apparatus, recording devices, and equipment that determine, affect, or measure control parameters are routinely calibrated, inspected, and checked on a predetermined frequency established in a written program based on their installation, operational, and performance qualification characteristics. All control systems should be verified for functionality and reliability.

F. Computer Control of Equipment

FDA's "Guide to Inspection of Computerized Systems in Drug Processing" (February 1983) and the "Guideline on General Principles of Process Validation" (May 1987) provide information useful to PET centers on designing, installing, validating, evaluating, operating, and controlling the automated, computerized and remote systems useful in the production of PET radiopharmaceuticals.

VI. COMPONENTS, CONTAINERS, AND CLOSURES

A. Regulatory Requirements

Subpart E in 21 CFR 211 (21 CFR 211.80 to 211.94) lists the requirements intended to ensure that components, containers, and closures:

1. Are suitable for use

2. Meet all necessary specifications at the time of use

3. Are adequately protected to avoid contamination, and

4. Do not impart impurities or other undesirable attributes into in-process materials. However, routine production and control procedures listed in Subpart E may not be specifically designed to remove or detect contaminants, impurities or other undesirable attributes in components, containers and closures

The requirements in Subpart E are further intended to prevent mixups and the accidental use of unapproved, unacceptable, or rejected components. Provisions of Subpart E cover the receipt, storage, handling, testing, approval or rejection, and disposition of components, containers, and closures. The record keeping requirements in Subpart E address courses of use for components, containers, and closures. It is essential to ensure the traceability of the component parts contained in the finished drug products as there may be questions, concerns, or recalls of the component parts at some later point in time.

B. Guidance

PET centers are expected to adhere to the requirements for component, container, and closure acceptance and use. There should be detailed written procedures to address the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures. Components, containers, and closures should be handled and stored in a manner designed to prevent contamination.

Bagged or boxed components of drug product containers, or closures should be stored off the floor and suitably spaced to permit cleaning and inspection. Each lot of components, containers, or closures should be identified with a distinctive code. These codes should be used in recording the disposition of each lot. Each lot should be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

Some examples of generally acceptable approaches to compliance, subject to confirmation of facility-specific appropriateness by FDA, are discussed below.

C. Coding, Identification, and Retesting

The manufacturer's (vendor's) immediate labeling plus a simple receiving log may suffice as the coding necessary for tracking control under 21 CFR 211.80(d) for finished articles and for hand-held-sized containers of bulk chemical substances. An appropriate identification as to status (i.e., quarantined, approved, or rejected) should be clearly marked on each item (e.g., bulk substance containers, shelf-pack of vials).

Retesting as described in 21 CFR 211.87 is not generally expected for finished articles that are used within their labeled expiration dating period and that have been stored as specified in their labeling. In such circumstances, adherence to the following procedural controls would be generally acceptable to comply with this section:

1. Stock containers are dated upon receipt.

2. Stock containers are tight and stored under proper environmental conditions, including temperature and humidity control and cleanliness.

3. Stock containers are opened and contents withdrawn under strictly controlled cleanliness of the immediate environment, utensils, and technique.

4. At the time of each use, the contents of stock containers are inspected for visual or other physical evidence of deterioration or other indication of unacceptable quality.

5. The contents of stock containers are used within a reasonable, not prolonged, period of time, as would be suitable in accordance with the stability characteristics of each particular component. The latter can be controlled by a system for writing appropriate dates on the label of each stock container.

Lot-by-lot retesting of [^{18}O] enriched water would not usually be expected if the longest intended or expected length of time of use of [^{18}O] enriched water is validated through appropriate testing in accordance with the methods stated in the approved DMF or NDA. Until consistency is achieved, each lot should be retested at the time of its last

use. Once consistency has been established, it may be acceptable to progressively reduce the frequency of retesting. However, lot-by-lot retesting should resume whenever there is a change in the supplier of [^{18}O] enriched water, or there is evidence of sufficient variability in the quality of a lot of [^{18}O] enriched water over time or the between-lot quality to warrant more intensive testing.

D. Finished Articles Used as Components or Container-Closure Systems

There may be some inherent limitations due to radiation safety considerations in the ability to visually inspect finished PET radiopharmaceuticals drug products. One acceptable approach for some PET radiopharmaceuticals ([^{15} O] or [^{11} C] compounds) might incorporate procedures to provide that: (1) Each component or container-closure system is inspected individually for visual evidence of particulate, foreign matter, and container-closure defects immediately before use; (2) defective components will not be used; and, (3) the batch production and control record of the PET radiopharmaceutical includes a signed or initialed verification that such inspection was conducted and that only acceptable finished articles were used.

E. Analytical and Identity Testing of Chemical Components

21 CFR 211.84 requires that each lot of critical components released for use meet all acceptance specifications for identity, potency, purity, and quality as specified in a drug application, DMF, and the master production and control records. These requirements are essential to the proper synthesis of the active ingredient as well as substances included in the finished product. The chemical, physical, and microbiological stability of the finished drug product, as well as components used to manufacture the product should be tested and documented.

If the initial acceptability of components is based solely on the data in supplier certificates of analysis (COA), 21 CFR 211.84(d) requires drug manufacturers to have suitable evidence establishing the consistent reliability of the supplier's analyses and to conduct at least one approved identity test per lot.

In PET drug manufacturing or when no compendial or approved identity test is specified for a specific component, a reaction-based testing procedure may be established, rather than instrumental testing. Such procedures would capitalize on the fact that if the wrong ingredients are used in the synthesis of the PET radiopharmaceutical, the intended step will not transpire and/or the finished product will not meet its specifications. For example, the method for confirming the identity of [^{18}O] enriched water might involve the testing of the [^{18}F]-Fluoride resulting from its bombardment.

F. Endotoxin Testing of Components

In conventional drug product manufacturing, the requirements of 21 CFR 211.84 states that each lot of each component should be tested to ensure that no lot of any component exceeds specified endotoxin limits. This approach assesses the amount of potential endotoxin that might be carried over to the finished drug product. It is acceptable to establish limits on the basis of tolerable potential carry-over quantities of endotoxin to the finished product. Acceptable means for endotoxin determination include certificates of analyses (COA), contract testing, and in-house testing.

It may be possible to forego endotoxin testing of components when endotoxins are removed by a validated process, such as endotoxin filtration, or when a valid endotoxin test cannot be established. Documented evidence for certain components that establish their inherent inability to support pyrogens may also eliminate the need for component testing for this attribute.

The synthesis processes for PET radiopharmaceuticals may be truly destructive to endotoxin (e.g., prolonged heating of an in-process fluid in strong acid or alkali). Endotoxin testing of any component entering the manufacturing process in advance of the endotoxin-destructive step may not be needed. Some synthesis processes having the capacity to destroy endotoxins should be documented and validated for each step in the manufacturing process. Endotoxin control as part of the synthesis process is discussed under Pyrogen (endotoxin) control in Section V on Equipment.

VII. PRODUCTION AND PROCESS CONTROLS

A. Regulatory Requirements

21 CFR 211.110 requires, in part, sampling and testing of in-process materials and drug products to ensure batch uniformity and integrity.

21 CFR 211.113 requires, in part, the establishment of and adherence to appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile. Such procedures should include validation of any sterilization process.

B. In-Process Sampling and Testing

FDA acknowledges that the sampling or testing of in-process materials may not be appropriate for PET radiopharmaceutical drug products due to radiation safety concerns, the short half-lives of positron emitting radionuclides, the synthesis apparatus, or a combination of these or other factors. Although it is important to

ensure in-process batch uniformity and integrity, alternative means may be considered for in-process sampling and testing. The intended purposes of in-process sampling and testing should be achieved, all equipment controlled and monitored, and parameters validated in the established manufacturing process that demonstrates and documents that the product has acceptable product release specifications.

Methods for in-process testing should be established in the master production and control records and documented in the batch production and control records. Checks and documentation can be manually performed, computer controlled, automated, or employ a combination of these processes. FDA's "Guide to Inspection of Computerized Systems in Drug Processing" (February 1983) and the "Guideline on General Principles of Process Validation" (May 1987) provide information that may be useful to PET centers for the design, installation, validation, evaluation, operation, and control of automated and remote systems used for process control.

C. Sterilizing Filtration

The sterilizing filtration process used in the manufacture of PET radiopharmaceuticals should be fully validated and controlled to ensure the sterility of the finished products on a consistent basis. The validation of a sterilization process involves planned testing designed to demonstrate that microorganisms will be effectively destroyed. All sterilization processes should be specified. Sterilization processes may include, for example, autoclaving to destroy and filtration to remove microorganisms. Once a method has been appropriately validated, these sterilization processes should be performed in a documented manner according to the control parameters in the written procedures.

Sterilizing by filtration should be capable of removing microorganisms from PET radiopharmaceuticals. It is generally accepted that a sterilizing filter is one that, when challenged with the microorganism *Pseudomonas diminuta* at a minimum concentration of 10^7 organisms per cm^2 of filter surface, will produce a sterile effluent. It is also generally recognized that a membrane filter having a nominal pore size rating of 0.2 μm or smaller is consistently capable of meeting this criteria for mobile aqueous liquids similar to PET radiopharmaceuticals. Therefore, a PET center can use a 0.2 μm membrane filter as a sterilizing filter for production. Generally, PET centers employ commercially available, sterile, preassembled, ready-to-use small (e.g., 25 mm diameter or smaller) filtration devices (ready-to-use filter devices) for product sterilization.

Before a PET radiopharmaceutical may be administered to patients, any filtration device used in its manufacture should have been shown to be:

1. Compatible with the product

2. Sized and suitably constructed for the intended filtration time, processing pressures, and associated use of the apparatus

3. Proven effective in sterilizing under the specified operating conditions for its use

Vendor certification of compatibility, suitability, and validation is acceptable.

Manufacturing process parameters including the filtration rate, pressure and duration, temperature, pH, viscosity, ionic strength, and osmolarity, may affect the effectiveness and integrity of filtration systems. Such factors may physically or chemically alter filter integrity, affect microbial capture mechanisms, or shrink the microorganisms. Hydrostatic shock and other system stresses should be taken into account during validation and controlled accordingly during processing.

Validation for the sterilizing process should be all inclusive (worst case situations) based on the specified limits for the product's characteristics, process parameters, and sterilization conditions that may affect the effectiveness and integrity of the filtration system.

After validation, the relationship between filtration effectiveness and specified processing parameters and conditions may be relied on. However, adequate process controls should be present in the manufacturing process to ensure that the validation limits are not exceeded during production.

Lot-by-lot integrity testing should be performed to ensure that the validated filtration device has performed acceptably during manufacture. For small-volume filtration using small ready-to-use devices, it may be acceptable to limit integrity testing to post-filtration. Acceptable test methods for quantitating filter integrity include bubble point, diffusing pressure-hold and forward-flow technologies.

D. Aseptic Processes

All aseptic processes should be validated before PET radiopharmaceuticals are manufactured and distributed. Examples of aseptic processes in the manufacture of PET radiopharmaceuticals include the assembly of the container-closure system, container-to-container transfers with a needle and syringe, and repackaging from a multidose vial into unit-dose syringes. Validation studies should be designed and conducted to document that sterile articles remain consistently uncontaminated during aseptic processing.

The media fill simulation technique involving the use of nutrient growth medium during

a simulated sterile product filling is a well-established approach in the validation of aseptic processing in pharmaceutical manufacturing. This is commonly referred to as *sterile media fills*.

The culture medium used in these media fill simulations should be capable of promoting the growth of a broad spectrum of microorganisms likely to be encountered as production-associated contaminants in the PET center. Commercially available sterile culture media, such as trypticase soy broth, suitably packaged for the PET center's validation requirements, may be used. A PET center may also use culture media prepared and sterilized in-house from reconstituted, commercially available powdered concentrates. In either case, growth promotion should be verified and documented for any media used.

USP methodology for growth promotion is generally acceptable for this testing. Incubation of medium-filled units for a minimum of 14 days, with the first 7 days at room temperature (20-25°C) and the final 7 days at 30-35°C is an acceptable methodology. The suitability of alternative incubation schedules should be scientifically justified by the PET center to ensure visibly detectable growth of any potentially contaminating microorganisms.

At least three consecutive, successful validation runs (no growth detected) should be performed before an aseptic process can be considered valid. All personnel should therefore perform at least three consecutive successful media fills for any unique aseptic operation. Similarly, at least three consecutive successful media fills should be performed for any operational or configurational change that might potentially contribute to microbial contamination during the aseptic process.

Any sterile media fill failure should be investigated promptly, including identification of the contaminating microorganism(s). At a minimum, this investigation should include:

1. The review of environmental monitoring data
2. The review of personnel practices
3. The review of their aseptic technique
4. The review of the production and environmental control procedures
5. The review of the cleaning, sanitizing, and disinfection procedures

Correction of possible causes for the failure of this test should be instituted promptly and should be fully documented.

Any person who fails to perform a media fill test successfully should perform at least three consecutive successful media fills before resuming routine aseptic processing. When a media-fill failure occurs, the PET center should conduct a complete, documented investigation to determine the possible causes and to take the most appropriate corrective actions previously described as soon as possible.

In each calendar quarter, personnel should successfully complete at least one sterile media fill simulation per assigned aseptic operation for continued qualification. The sterile media fill technique is also suitable for the validation of aseptic processing in PET radiopharmaceutical manufacturing. The validation procedure should be representative of routine production under environmental conditions that simulate actual and preferably worst case conditions established as quality limits for production.

To achieve this, the validation procedure could include but not be limited to:

1. Encompassing and approximating as closely as possible all parts, phases, steps, activities, conditions, and characteristics of the routine process where components, fluid pathways, in-process fluids, etc., are expected to remain sterile.

2. Considering all potential sources of microbial contamination during processing.

3. Accounting for all manipulations, handling, environmental conditions, and other factors that might influence the risk of process-associated contamination. The intensity of challenges should be no less than the greatest risk that would be encountered during routine production (e.g., the maximum number of assemblies prepared at one sitting).

4. Imposing the most rigorous challenges to operator technique. This is particularly important in manual aseptic processes, which may be employed in some PET centers. Production personnel should be expected to conduct media fills under the same conditions as those encountered in actual production (i.e., under the same level of fatigue, stress, and pace encountered in the most intense conditions of routine production.)

5. Performance under the conditions of environmental quality equivalent to routine production and preferably including worst case situations.

6. Requiring the processing of no less than the maximum number of units processed during the most intensive production schedule actually employed.

Environmental and personnel monitoring should be performed during the validation

process. The methods used and the quantity of data collected during the validation process should be sufficient to establish appropriate monitoring parameters and limits for routine production.

VIII. PACKAGING AND LABELING CONTROL

A. Regulatory Requirements

21 CFR 211.122 to 211.134 contain numerous requirements intended to ensure that finished drug products are accurately labeled. These requirements deal with the receipt, identification, storage, handling, sampling, examination, and testing of product labeling and packaging materials; labeling issuance; packaging and labeling operations; and drug product inspection. However, the requirements contained in 21 CFR 211.132 for tamper-resistant packaging for over-the-counter (OTC) human drug products are not included in this guidance because PET radiopharmaceuticals are not OTC drugs.

B. Guidance

FDA acknowledges that the ways in which packaging and labeling are accomplished in the manufacture of PET products differ appreciably from these functions in conventional drug pharmaceutical manufacturing. For example:

1. Labels for PET radiopharmaceutical drug products may be printed on the day that the lot is manufactured and in quantities limited to the manufactured lot and its production records.

2. The printed label typically contains lot-specific information entered into the computer at the time of printing, as well as product-specific template information retrieved from a computer file.

3. Printed labels may be manually affixed one by one to each article.

4. Because of radiation safety considerations the immediate product container may have to remain continuously within its lead shielding (commonly referred to as a *pig*) from the end of the synthesis process until such time (i.e., sufficient half-lives) have transpired to allow the safe removal of the vial from the pig. A requirement to affix a label to the immediate product container would not be warranted based on risks associated with possible radiation exposure.

Although the application of specific regulatory requirements for certain aspects of the packaging and labeling of PET products may necessitate some special interpretation,

such operations are still expected to comply with statutory CGMP requirements and the full *intent* of the CGMP regulations.

PET centers are expected to have appropriate written procedures for labeling along with examples of these approaches. Labeling controls should ensure the following:

1. Label contents are accurate.

   a. 21 CFR 211.122(a) requires, in part, that there be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling. For computer-generated labels produced at the time of use, there should be policies and procedures that allow only authorized personnel to generate labels (e.g., the computer may have a lockout system to prevent unauthorized label generation. In addition, labels should be prepared for only one lot at a time and only in quantities sufficient for that lot.)

   NOTE: FDA's "Guide to Inspection of Computerized Systems in Drug Processing" (February 1983) should be consulted for guidance pertaining to computer-generated labels.

   b. 21 CFR 211.122(a) further requires, in part, that those labeling materials should be representatively sampled and examined or tested before use. In addition, 21 CFR 211.125(b) requires that labeling materials issued for a batch should be carefully examined for identity and conformity to the appropriate specified labeling. For computer-generated labels produced at the time of use, both requirements may be met by examining the labels when they are generated to assure their correct identity and conformity. These labels should be compared to the appropriate approved master labeling and should be documented.

2. Each container has the correct label affixed to it.

   Section 211.130 specifies a number of requirements designed to ensure that correct labeling is applied or affixed to each container of drug product. The following special procedure could be used by preparing two types of labels per lot:

   a. Although a complete lot-specific finished product label should be affixed to the pig containing the filled multiple dose vial, an incomplete label may be affixed to the pig prior to the PET product filling the vial. Information such as activity may be written directly onto this label by hand after filling.

b. A lot-identifying pre-label, which may be identical to the incomplete label affixed to the pig, may be affixed to the unfilled multiple dose vial before placing it in the pig.

i. In this circumstance, an incomplete label identical to that affixed to the pig is incorporated into the batch production record. The information necessary for label completion is written simultaneously on the pig label and the label in the production record so that both are identical. If different from the incomplete label affixed to the pig, a duplicate of the lot identifying vial label should also be incorporated into the batch production record.

ii. There is written verification that no old label appears on the pig (which may be reused indefinitely) when the new label is affixed [21 CFR 211.130(e)].

iii. One of the conditions of lot release is that a second person

- verify the accurateness and completeness of the label contents
- verify the placement of the correct label on the corresponding container or pig

Verification should be documented on the production batch and control records.

Such a system conforms to 21 CFR 211.122(g)(3), which describes special control procedures required when cut labeling is used.

Further details concerning regulatory requirements for individuals performing second person verification are contained in 21 CFR 211.25. The second person performing these tasks should have received adequate training to successfully fulfill the task.

Adequate training for such individuals should include the ability to discriminate with 100 percent accuracy between correct and incorrect labeling and the knowledge and ability to take appropriate action in either instance. Where labels are affixed to their respective pigs by a second person, training should also include the ability to discriminate between correct and incorrect containers.

3. Labeling mixups are avoided.

a. The second person should allow no delay between proofreading and affixing the label, and the label should not leave his or her hands between these tasks. This practice should avoid label mixups in situations where the second person affixes labels to their respective pigs after proofreading these labels.

b. Section 211.122(d) includes certain storage requirements for labeling, intended to preclude label mixups. All appropriate measures should be taken to handle labels in a manner that minimizes the risk of mixups with any other labeling materials.

4. Adequate lot-specific packaging and labeling records are maintained as required by regulations.

a. Labeling records must be maintained (e.g., by examining packaging and labeling materials (21 CFR 211.130(d)).

b. The packaging and labeling facilities must be inspected (21 CFR 211.130(e)).

c. Batch production and control records must be maintained (21 CFR 211.188(b)(6) and (b)(8)).

IX. HOLDING AND DISTRIBUTION

A. Regulatory Requirements

Written procedures are required for the warehousing of quarantined drug products, for drug product storage under appropriate conditions, and for distribution [21 CFR 211.142 and 21 CFR 211.150].

B. Guidance

The written procedures specified in 21 CFR 211.142 for warehousing and in 21 CFR 211.150(a) for distribution need to be appropriate for the activities of the PET centers and their manufacture and distribution of PET radiopharmaceutical drug products.

There should be written procedures to ensure that drug products are not distributed before they are released, as required by 21 CFR 211.142(a). These procedures should ensure that the products are held, however briefly, under appropriate conditions that

will not adversely affect them (21 CFR 211.142(b)).

In accordance with 21 CFR 211.150(b), at least a simple distribution log documenting the date and destination of each lot of PET drug product should be maintained and kept current.

X. TESTING AND RELEASE FOR DISTRIBUTION

A. Regulatory Requirements

21 CFR 211.165(a) requires that for each manufactured batch of drug product, there should be appropriate laboratory determinations to establish conformance with that drug product's final specifications prior to release.

21 CFR 211.167(a) requires that for each batch of drug product purporting to be sterile and/or pyrogen-free, there should be appropriate laboratory testing to establish conformance. However, 21 CFR 211.165(a) permits release of specific batches of short-lived radiopharmaceuticals before completion of sterility or pyrogen testing, provided that such testing is completed as soon as possible.

B. Release Testing

Each lot of a PET radiopharmaceutical should be tested and should conform with written, approved test parameters that generally include color, clarity, radiochemical purity, radiochemical identity, specific activity, total activity, radionuclidic purity, radionuclidic identity, chemical purity, and pH. The short half-lives of PET radiopharmaceuticals may preclude the completion of all tests prior to product release. In such circumstances, the sponsor should establish all testing procedures, including methods, specifications, and validation of these methods, in the NDA.

Sterility and/or pyrogen tests should be conducted for injectable PET drug products. However, such injectable PET radiopharmaceutical drug products may be released prior to completion of these tests provided such tests are completed as soon as possible. The sections on Sampling and Sterility Testing Methodology will discuss sterility testing in more detail.

C. Sampling

When a lot or batch of drug product consists of a single container of a PET radiopharmaceutical, approaches that provide a representative sampling of the container's contents can be used. A sampling procedure should not create contamination risks to the remaining contents. For example, the vial stopper of a

finished drug product should not be penetrated with a needle and a syringe unless in an environment that is maintained in Class 100 conditions.

Following are some acceptable approaches for sampling (this is not an exclusive list of examples):

1. A syringe and needle are aseptically attached to the vial as part of the container assembly. After the filled vial is detached from its filling needle, the sample is drawn directly into the syringe. The needle is then quickly removed from the stopper. This final step should be conducted as an aseptic process in the critical area.

The critical area should be maintained in Class 100 conditions (in an LAFW, positive pressure glove box, or other contained atmosphere) and provided an effective airborne microbial control. The exposed needle, once withdrawn from the stopper, creates an opportunity for microbial contamination of the sample. Therefore, an aliquot of the sample should be taken for sterility testing.

2. A 0.2 μm membrane filter and needle could be aseptically attached to the vial as part of the container assembly. After the filled vial is detached from its filling needle, a syringe is directly attached to the filter, and a sample is drawn into the syringe through the filter. Aseptic technique is not required for these steps.

An aliquot from this sampling should be taken for pyrogen testing to ensure that endotoxins are not retained or inactivated by the filter. An aliquot of this sampling should not be taken for sterility testing because of filtering of the sample.

3. After production, the final container could be punctured with a needle and syringe to withdraw the samples. This technique should be conducted as an aseptic process in a Class 100 environment. Furthermore, this aseptic process should be validated to ensure that the remaining contents of the vial do not become contaminated as a result of this invasive procedure.

D. Sterility Testing Methodology

As an alternative to the sampling approaches listed above, the following approach using a proxy container can be used for the sterility testing of single container lots.

For each lot of PET radiopharmaceutical, the production container and a proxy container are aseptically assembled side-by-side. The proxy container should be exposed at the same time and to the same aseptic assembly steps as the production

container. However, the aseptic addition of sterile diluent to the production container is simulated by the aseptic addition of an equivalent volume of sterile Soybean Casein Digest Medium into the proxy container.

Note that the volume of medium added to the proxy container should be appropriate:

- To visualize any subsequent microbial growth
- To prevent interference of growth due to excessive dilution of the sample.

Sterile equipment (filter devices, needles, stoppered vials, airway vent filters) should be used for the proxy sample. Furthermore, the sterile items should come from the same lot used in the manufacture of the companion lot of the PET radiopharmaceutical drug product. The interior of the proxy container is considered to be microbiologically representative of the interior of the production container for purposes of sterility testing.

Aseptic container assembly should be designed to achieve a fluid pathway configuration appropriate for the sterility test sampling procedure. Using a Y-type sterile tubing device, for example, the sterile fluid pathway leading from the sterilizing filter will divide into two branches. One branch leads into the production container and the other into the proxy container. Pinch clamps or equivalents are affixed to each branch for a proper diversion of the sterile fluid. After the production container has been filled with active ingredients, the line to the production container is closed and the line to the proxy container is opened. Caution should be exercised to ensure that undesired fluid does not gain unintentional entry into the production container. The needle should be removed from the production container as soon as this line is clamped.

A volume of fluid equal to the volume in the production container should be advanced through the sterilizing filter and the proxy container as a sterility test sample. It is not necessary for this fluid to contain the PET radiopharmaceutical drug product.

The proxy container should be equipped with a sterile vent filter and incubated at room temperature (20-25°C) in an upright position for a minimum of 14 days. The contents of the proxy container should be observed and results recorded daily for growth. Observations and documentation are not required on nonproduction days or on days when personnel are not normally present in the facility.

The sterility testing procedure used by PET centers should be properly validated to ensure the reliable detection of growth of possible microbiological contamination of PET radiopharmaceuticals.

If the results of any sterility test are positive for microbial growth, a complete investigation should be conducted immediately. Corrective actions based on the results of the investigations should be implemented before further production. For further information on the investigation of sterility test failures, please see FDA's "Guideline on Sterile Drug Products Produced by Aseptic Processing" (June 1987), pp. 36-41.

A sterility test result that is positive for microbial growth is highly suggestive of inadequate operator technique. All aspects of the manufacturing process should be investigated thoroughly. Any operator involved in any aseptic process where a sterility failure is documented should be requalified in each step of the aseptic process (e.g., container assembly, aseptic attachments, content sampling, sterility test sampling). Requalification should occur before any operator is allowed to perform aseptic processes involving the production lots.

XI. STABILITY TESTING AND EXPIRATION DATING

A. Regulatory Requirements

21 CFR 211.166 requires, in part, a written testing program designed to assess the stability characteristics of drug products and the use of such results to determine appropriate storage conditions and expiration dates. This section includes certain requirements for the written program, such as appropriate test intervals and adequate number of test batches. Section 211.137 requires that drug product should bear expiration dates that have been determined by appropriate stability studies.

B. Guidance

For each PET radiopharmaceutical drug product, PET centers should establish minimal standards below which the product would be considered to be unsuitable for use (see Section X on Testing and Release for Distribution for guidance covering content testing).

The stability plan for each PET radiopharmaceutical should incorporate those parameters stated in the approved drug application. In establishing and verifying the real-time stability for a drug product, PET centers should dedicate three initial lots of a PET radiopharmaceutical to this purpose. The expiration date/time assigned to each lot (expressed as the date, the hour, and the minute beyond which the PET radiopharmaceutical cannot be used) should ensure that at least the minimum specified limit for each specified content parameter will be present at that time.

The drug product's stability characteristics should be reflected in the product's labeling. Observed and measured parameters for testing for a drug product's acceptability, stability and expiration dating are specified in the corresponding approved new drug

application. Further guidance may be found in FDA's "Draft Guideline for Submitting Supporting Chemistry Documentation in Radiopharmaceutical Drug Applications" (November 1991).

Generally, annual stability testing is recognized as good manufacturing practice for conventional drug products, under the provisions of 21 CFR 211.166. This requires the testing of an adequate number of batches to determine an appropriate expiration date. Due to the short life of PET drug products and the nature of radioactive decay, FDA would expect PET centers to revalidate a PET radiopharmaceutical's stability annually, as part of its normal, routine production.

XII. RESERVE SAMPLES

A. Regulatory Requirements

21 CFR 211.170(a) requires the retention of reserve samples representative of each lot in each shipment of each active ingredient. 21 CFR 211.170(b) requires the retention of reserve samples of each lot of drug product. These regulations further specify the quantity, manner, and duration of storage, as well as examination of reserve samples.

B. Guidance

Some PET centers may consider one or more of these reserve sample requirements to be inappropriate or unfeasible due to lot size limitations, to short physical half-lives, radiation safety issues, and the nature of the synthesis process for active ingredients.

When the proposed rule for alternatives and exceptions to CGMP requirements is finalized, PET centers may wish to apply to the Agency for an exception or alternative in accordance with this rule. For example, an exception to the requirement to keep reserve samples for each lot of finished PET drug product might be appropriate when the entire lot consists of only one vial of product.

XIII. YIELDS

A. Regulatory Requirements

21 CFR 211.186(b)(7) requires the inclusion of a statement in master production and control records regarding theoretical production yields and establishing a maximum and a minimum percentage of theoretical production yields). Similarly, 21 CFR 211.188(b)(7) requires the inclusion in batch production and control records of a statement of actual yields and a statement of the percentage of theoretical yields at

appropriate phases of processing. The actual yields and percentages of theoretical yields should be determined at the conclusion of each appropriate manufacturing phase (§ 211.103).

21 CFR 211.101(a) requires that a batch should be formulated with the intent to provide not less than 100 percent of the labeled or established amount of an active ingredient.

21 CFR 211.192 requires a thorough investigation for any unexplained discrepancy noted on review of the batch production and control record. This requirement includes the situation where the actual percentage production yield exceeds the maximum or minimum percentages of a theoretical production yield as established in the master production and control records.

B. Guidance

PET centers should define the acceptable range for the intended (theoretical) yield in their master production and control record prior to the actual manufacturing of a PET radiopharmaceutical drug product.

It is acceptable to have lot-to-lot variation in intended yields within ranges as specified in the master production and control record. With manufacture of each lot, theoretical and actual yields should be compared. If the actual percentage yield falls outside the specified range, an investigation into possible errors or loss of process control should be conducted.

FDA acknowledges that acceptable ranges for theoretical yield for PET drug products may be wider than generally encountered in conventional pharmaceutical manufacturing. However, the specified range should be narrow enough to detect potential manufacturing problems or errors. The acceptability of a range of theoretical yields should be justifiable on the basis of the facility's historical product-specific batch production and control records. This range should be established based on scientific evidence and should never be made on empirical judgments or arbitrarily.

XIV. SECOND-PERSON CHECKS

A. Regulatory Requirements

Several CGMP regulations require a second person to examine, observe, verify, or check various functions (collectively termed *checks*) performed by another person. Such requirements include:

1. Independent checking, dating, and signing by a second person of master

production and control records for each drug product [21 CFR 211.186(a)].

2. Independent verification of correct labeling by 100-percent examination for hand-applied cut labeling [21 CFR 211.122(g)(3)].

3. Examining components and verifying their addition to the batch [21 CFR 211.101(c) and (d)].

4. Verifying calculations of yields [21 CFR 211.103].

5. Checking significant manufacturing steps [21 CFR 211.188(b)(11)].

6. Reviewing original laboratory records [21 CFR 211.194 (a)(8)].

7. Double checking the cleaning and maintenance of equipment [21 CFR 211.182].

B. Guidance

Although some PET centers, especially single operator PET facilities, may question their ability to comply with second-person checks, FDA believes these requirements are essential to minimizing the possibility of undetected human error. Therefore, all PET centers are urged to establish a systematic approach for meeting second-person check requirements.

21 CFR 211.25 describes the regulatory requirements for individuals designated to perform second person tasks. 21 CFR 211.25 further requires that each second person should receive adequate training to perform these tasks.

There is a broad pool of potential personnel who can perform second-person checks. In a medical center, it might be feasible to train personnel from other departments to perform these checks on an as-needed basis available to the PET center. The independent checking of master production and control records [21 CFR 211.34] might also be performed by a qualified consultant.

The requirement for second-person verification of hand-applied cut labeling was described in Section VIII, Packaging and Labeling Control. Verification of all checks should be signed or initialed at the time the check actually is performed.

XV. RECORDS AND REPORTS

A. Regulatory Requirements

21 CFR 211.196 requires distribution records to contain certain information about the distribution of drug products.

21 CFR 211.184(c) requires an individual inventory record of each component, drug product container, and closure, and, for each component, a reconciliation of the use of each lot of such component.

B. Guidance

For PET products distributed only to their radiopharmacy or nuclear medicine service in the same medical center, medical complex, hospital, or other clinical building in which the PET center is located, the requirement for distribution records in 21 CFR 211.196 could potentially be achieved with general statements in standard operating procedures identifying the specific drug products and the locations to which those drug products are distributed.

Some PET centers may question the need to meet all of the requirements of 21 CFR 211.184(c) for inventory and reconciliation records of components, containers, and closures used in the finished drug product, as defined in Section VI, Components, Containers, and Closures. PET centers may wish to apply to the Agency for an exception or alternative in accordance with the rule discussed in Section I of this guidance. Such a request might take into account the small quantities involved and the degree to which the information required by 21 CFR 211.184(c) might be readily traceable from other available records including receiving logs and batch records.

XVI. REFERENCES

U.S. Department of Health and Human Services, Food and Drug Administration (FDA). 1983. *Guide to Inspection of Computerized Systems in Drug Processing*. February 1983.

FDA. 1987. *Guideline for Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices*. December 1987.

FDA. 1987. *Guideline on General Principles of Process Validation*. May 1987.

FDA. 1987. *Guideline on Sterile Drug Products Produced by Aseptic Processing*. June 1987.

FDA. 1991. "Draft Guideline for Submitting Supporting Chemistry Documentation in Radiopharmaceutical Drug Applications," FOD Doc. No. 2009. November 1991.

ATTACHMENT A

GLOSSARY OF TERMS

The following terms associated with the manufacture of PET radiopharmaceuticals are used in this guide:

Active ingredient: any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. 2-Deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]-FDG) used in the manufacture of FDG Injection is an example of an active ingredient.

Batch: a specific quantity of a drug or other material that is intended to have uniform character and quality, within specific limits, and is produced according to a single manufacturing order during the same cycle of manufacture. In the case of PET radiopharmaceuticals manufacturing, the material produced during a single irradiation cycle using a synthesis and/or purification operation would constitute a batch.

Component: any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

Controlled environment: an area that provides consistent, specified environmental conditions with defined limits, maintained as limited-access, and providing appropriate environmental monitoring.

Critical area: an area in which sterilized dosage forms, containers, and closures are exposed to the environment, particularly the environment immediately surrounding aseptic-processing activities and critical surfaces.

Critical surface: a surface that comes into contact with sterilized products, sterile containers, or sterile closures.

Drug product: a finished dosage form that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient, but is intended to be used as a placebo.

In-process material: any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.

Lot: a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits. Or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that ensures it has uniform character and quality within specified limits.

Positron emission tomography (PET): a medical imaging modality used to assess the body's biochemical processes. Radionuclides are manufactured into PET radiopharmaceutical drug products that are then administered to patients for medical imaging. The medical images of the body's biochemical processes are then evaluated, generally, for diagnostic purposes.

PET center: a drug manufacturing facility that produces and distributes PET radiopharmaceuticals. The manufacturing process generally involves the generation of a radioactive postbombardment substance (radionuclide) resulting from the bombardment of a target material by a particle accelerator. The radioactive postbombardment substance is then directly used in chemical synthesis to manufacture a PET drug product under current good manufacturing practices. These PET centers are usually, but not necessarily, located in medical centers or hospitals. The normal daily batch production is usually performed by a multidisciplinary team involving a broad range and level of personnel with appropriate training and experience in radiopharmacy, radiochemistry, nuclear physics, manufacturing and testing of PET radiopharmaceuticals.

PET radiopharmaceutical drug product: a finished radioactive drug product in its final container suitable for distribution. It contains an active ingredient typically in an aqueous system intended for use in PET. The product may or may not include other components, such as sodium chloride for isotonicity or a buffer system for pH control. Fludeoxyglucose F 18 Injection (FDG Injection), Fluorodopa F 18 Injection, and Sodium Fluoride F 18 Injection are examples of liquid injectable PET radiopharmaceuticals.

Positron (β^+): a particle emitted from the nucleus with the same rest mass as an electron but with a positive charge. It is considered to be the antimatter counterpart to the electron.

Positron decay: the emission of positrons from a neutron-deficient and unstable nucleus. The positron has a kinetic energy that carries it through matter. When the positron is almost at rest, it collides with an electron and is annihilated, resulting in the emission of two γ-rays of equal and specific energy (511 keV-equivalent to the rest mass of an electron) in almost exactly opposite directions (180° to conserve near zero momentum). Positron emission effectively creates a neutron from a proton.

Positron-emitting radionuclides: radioactive atoms that decay by partial or total emission of positrons. They are created by the reaction with accelerated particles, produced in a particle accelerator, reactor, or other charge-particle accelerator, on stable target nuclides. [^{18}F]-Fluorine, [^{11}C]-Carbon, [^{13}N]-Nitrogen, and [^{15}O]-Oxygen are examples of positron-emitting radionuclides associated with liquid injectable PET radiopharmaceuticals.

Radioactive postbombardment substance: the material, usually liquid, which contains positron-emitting radionuclides, that is delivered to the reaction apparatus for synthesis of an

active ingredient as an integral part of the manufacture of a PET radiopharmaceutical drug product. [^{18}F]-fluoride or [^{11}C]-labeled precursors for the production of organic [^{18}F] or [^{11}C] active ingredients (e.g., 2-deoxy-2-[^{18}F]fluoro-D-glucose) are examples of these substances.

Target material: a substance in gas, liquid, or solid state to be irradiated by a beam current of charged-particles originated in a cyclotron, or other charge-particle accelerator. It contains the nuclide that will undergo the desired nuclear reaction to yield the positron-emitting radionuclide. [^{18}O] enriched water ([^{18}O]$H_2$0) is an example of a target material; it yields upon bombardment the ^{18}F-fluoride radioactive postbombardment substance used in the manufacture of FDG Injection. Other examples of target materials used for liquid injectable PET radiopharmaceuticals include N_2, Ne, H_2O, N_2(5% H_2), and CH_4. The terms *isotopic composition* and *purity of the target material* refer to the relative percentages of the principal isotope and other isotopes or elements present in the target material. Examples of target material impurities include [^{16}O] residual in [^{18}O] enriched H_2O targets, or traces of Cr, Fe, Co, F, etc., in any water target.

Target unit: the holder containing the target material. Its body is usually built of stainless steel or aluminum with inlet/outlet ports, a surrounding coolant system, and usually a thin foil target window, such as titanium foil.

ATTACHMENT B

Half-Lives of Positron-Emitting Radionuclides Useful or Potentially Useful in PET Radiopharmaceuticals

^{18}Fluorine -- 109.7 minutes
^{11}Carbon -- 20.4 minutes
^{13}Nitrogen -- 9.96 minutes
^{15}Oxygen -- 2.07 minutes

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

October 24, 1996

On March 21, 1995, the Food and Drug Administration (FDA) held a public workshop entitled "Positron Emission Tomography (PET) Regulatory Workshop." During the course of the workshop, many members of the audience asked questions about a variety of issues related to the regulation of PET drug products.

In an effort to address these questions, staff members in the Offices of Generic Drugs, Compliance, and Review Management in the Center for Drug Evaluation and Research have developed answers (see attached).

The FDA understands that questions about the regulation of PET products will continue. Therefore, the Agency is undertaking additional efforts to facilitate the dissemination of information on PET drug products to industry and the public. Planned activities include a second public workshop in early 1997, and several guidance documents.

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October 24, 1996

PET Questions and Answers from March 21, 1995 Workshop

Q1: In your transition plans, how can you ensure that this will not be disruptive to the delivery of health care in PET centers? How will financial devastation for the practitioners and other individuals and hospitals that have made these investments in these clinical care facilities be avoided?

A: During the implementation period, we did not take regulatory action against any PET facility and we do not expect to take action against any PET facility that demonstrates a good faith effort to comply with FDA regulations by developing a well-designed written plan or procedure with reasonable and defined time frames.

Q2: Will the FDA waive the user fees for all PET facilities?

A: Many new drug applications from PET facilities will qualify for the small business exception or other waiver under the Prescription Drug User Fee Act (21 U.S.C. 379h(b)(2) or 379h(d)). ANDAs are not assessed user fees under current law. For information on how to apply for the small business exception or a waiver see Interim Guidance Document for Waivers and Reductions in User Fees, July 16, 1993, and Supplement, February 1, 1995 (a copy of this document can be obtained from the Industry Liaison Office, Office of External Affairs, by calling 301-827-3430).

Q3: Within 18 months, you want every PET facility to file at least an IND, NDA, or an ANDA for every tracer that they are using. Are you looking for an IND, NDA, or an ANDA from each facility for each use of FDG?

A: More than one clinical indication or use can be studied under a single IND application for a single drug. One NDA or ANDA may be approved for multiple manufacturing sites, as long as it contains information on each manufacturing site. Several separate institutions or PET facilities may wish to consider the submission of a single application that could cover multiple manufacturing sites.

Q4: How are you going to regulate what is currently being used in clinical practice?

A: PET facilities, like other drug manufacturers, are required to comply with the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act). FDA has published guidance and policy statements interpreting FDA regulations to facilitate this process. Furthermore, FDA staff are ready to help any applicant in meeting the legal requirements. At a minimum, the FDA would like to see a good faith effort from the nuclear medicine and PET communities to comply within a reasonable and defined time frame according to a well-designed written plan or procedure. If the FDA determines

that a good faith effort is being made, the FDA does not intend to prevent the use in clinical practice unless a safety problem is identified.

Q5: *Most of the PET radioligands that we use have specific activities in the range of 1 curie/micromole. There really aren't very many low molecular weight compounds that would cause a pharmacological effect, let alone a toxicological effect in a human if given in a dose of 5 micrograms. Could FDA dispense with the requirement to provide toxicological information for PET drugs that don't have pharmacologic activity? Could limits (such as a specific activity of 1 curie/micromole) be set by which toxicological information could be eliminated?*

A: It would be difficult to establish a dose limit. A ligand could be highly selective and highly specific and go to receptors in a patient who already may be compromised with that receptor subtype. Agonists, and perhaps some antagonists, may have clinical effects at nanomole levels. Too many variables would have to be evaluated for each drug to set a standard dose for which no toxicological information would be needed.

Q6: *A pharmacological/toxicological waiver was granted for the one approved NDA for F-18 FDG. A literature survey was collected and circulated within the PET community. Is this an acceptable way to proceed until FDA provides additional guidance on this issue?*

A: Requirements could be waived for pre-clinical pharmacological/toxicological animal testing for other PET products based on the appropriate literature. For information on specific requirements for particular products, contact the Division of Medical Imaging and Radiopharmaceutical Drug Products in the FDA, Center for Drug Evaluation and Research.

Q7: *(a) If there is a successful ongoing IND, could it be used to support other new INDs for the same drug? (b) Would other clinical trials support a new IND for the same drug? (c) Would it be possible to reference another IND if authorization to reference is provided? (d) Could that alleviate the need to provide pharmacological/toxicological information in the second IND?*

A: (a) Yes, if it can be shown that the final drug products are equivalent, and if the sponsor obtains authorization to reference the data in the original IND.

(b) Yes, if it can be shown that the final drug products are equivalent, and if the sponsor obtains authorization to reference the data in the original IND.

(c) Yes.

(d) Yes, if the original IND contains adequate pharmacological/toxicological

information that is relevant to the second IND, the two drug products are equivalent, and the sponsor of the second IND obtains authorization to reference the data in the original IND.

Q8: Elaborate briefly on how GLPs might impact on a hospital-based or institutionally-based laboratory that wanted to do some animal pharmacology/ toxicology studies.

A: The Good Laboratory Practice regulations (21 CFR Part 58) apply the principles of quality assurance to toxicity (safety) testing. To ensure the quality and integrity of data submitted in safety studies performed as part of an IND or NDA, FDA requires compliance with the GLP regulations.

Some laboratories may want to conduct animal pharmacology studies. However, not all animal pharmacology studies are required to be performed according to the GLP regulations. Therefore, the effects of the GLP regulations will vary from facility to facility. Some laboratory facilities may already be in compliance; others may not. Furthermore, the GLP regulations allow IND and NDA sponsors to use consulting laboratories, contractors, or grantees to perform analyses or other services provided their work is done under the GLP regulations.

Q9: Most of the new PET compounds being developed are actually based on other compounds that are already used in patients. The difference is replacing a hydrogen atom by a carbon atom. Do we have to go through all these pharmacological procedures that have already been validated and for which literature is available?

A: If an atom on the molecule is changed, the possibility of a change in the toxicologic or pharmacologic profile of the drug exists. Even the distribution of the molecule could change. Because of this, data should be submitted for the changed molecule. If sufficient literature is available for the analog drug, new pre-clinical studies may not be necessary.

Q10: When making a compound with a specific radioisotope, and the pharmacologic and toxicologic profiles are known, do you have to repeat the pharmacological and toxicological studies if only the radioisotope is changed?

A: No. If sufficient data have been collected and submitted to the Agency for one chemical molecule, we generally assume that changing the radioisotope (e.g., 127 I to 131 I) would not change the pharmacologic and toxicologic profile. In contrast, changing H to 18 F would most likely affect the biologic profile.

Q11: There is one approved NDA for F-18 FDG. How will it be determined that other F-18 FDG products are the same as the approved product?

A: In reference to ANDAs, the regulations state that the generic product must be the same as the innovator product as follows:

- active ingredient
- dosage form
- route of administration
- strength

The regulations [21 CFR 314.94(a)(iii)] also require injectable products to contain the same inactive ingredients in the same concentration as the innovator. However, a parenteral product may differ in preservatives, buffers, or antioxidants as long as the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the drug product. Examples of the type of information that would describe "safety" are journal articles or reference to other approved parenteral products that contain the inactive ingredient. It should be noted that the concentrations for preservatives, buffers, or antioxidants in generic products cannot exceed the amount previously approved in a parenteral drug product.

Studies to show bioequivalence of F-18 FDG will not be required as long as the generic product uses the same inactive ingredients in the same concentrations as the innovator. Again, certain changes in preservatives, buffers, or antioxidants as described above may be permitted when seeking a waiver from the requirement to conduct a bioequivalence study. Any differences in formulation will be evaluated on a case-by-case basis to determine if a waiver of bioequivalence studies is acceptable.

Q12: There is good literature and scientific validation for some of the PET drugs. Can this data be used as a comparator?

A: Data from published literature that has been interpreted and analyzed properly may be adequate to support an application. It will depend ultimately on the strength of the data and its relevance to the application it is being used to support.

Q13: Can an application consist of one prospective and one retrospective study to support an indication?

A: Assuming they were done correctly, it would be acceptable to have both prospective and retrospective data. Although the results of two adequate and well-controlled studies are the standard submission, it is not necessary to complete two prospective clinical trials when existing data provide the information that is needed in a clinical trial. If existing data are used to support an application, the data should simulate the two trial design. However, the applicant should discuss the trials with the Agency prior to submission and the data would have to be evaluated before the application

could be approved.

Q14: Could the authors of published literature be contacted to supplement the published data with specific information that may be needed to support the approval of an application?

A: Yes.

Q15: Who is responsible if CGMP violations are found?

A: The individual or individuals who have the authority and responsibility for the operation(s) of drug manufacturing and distribution are responsible for compliance with FDA regulations.

Q16: From a regulatory perspective, if the holder of an approved NDA would supplement the NDA with another manufacturing site, who is responsible for the adverse event reporting for the NDA?

A: The NDA holder is responsible for submitting adverse reaction reports to the FDA.

Q17: Regarding the Federal Register notice for the proposed CGMP rule, we would have to double the number of staff people to meet the draft CGMP guideline. The estimated times required to complete the paperwork for annual reports have been grossly underestimated. How are small centers expected to meet the requirements? Will each NDA require an annual report?

A: Each ANDA/NDA will require an annual report, but annual reports vary in size. The reporting requirements are found in 21 CFR 314.80 and 314.81. If several sites are covered by the ANDA/NDA, only one cumulative report is needed.

Q18: What are the differences between exceptions, alternatives, exemptions, and waivers?

A: In the CGMP context, the FDA has indicated in the draft CGMP guideline that it will entertain requests for exceptions and alternatives to the CGMP regulations. An exception would be requested when the regulation cannot be meaningfully applied to PET drug manufacturing. An alternative would be requested when a different method could be substituted for the accepted method. The terms "exemption" and "waiver" do not apply in this context.

Q19: Is there a different set of regulations for small-scale versus large-scale manufacturing?

A: No. Although the regulations (21 CFR Parts 210 and 211) do not distinguish between small-scale and large-scale manufacturing, certain site-specific activities and practices may qualify for an exception or alternative.

Q20: Does the FDA intend to publish which waivers, exceptions, exemptions, and alternatives have been granted?

A: Periodically, the Agency will publicly disseminate information on the types of exceptions and alternatives it has granted.

Q21: When preparing ANDAs, if we know that one applicant has obtained an exception, can we assume we will also receive the exception?

A: Exceptions and alternatives must be requested and justified on a case-by-case basis. The FDA will make every possible effort to treat like situations alike.

Q22: Could exceptions be classified according to what cyclotron system you are using and similar black box setups?

A: Current good manufacturing practices apply to manufacturing processes and not to individual pieces of equipment. Similarly, exceptions and alternatives to the CGMPs will likely apply to manufacturing processes. It is hard to predict what logical grouping could be made until we see the actual applications. It is conceivable, but we will have to wait and see what mechanism is possible.

For example, sampling and testing of in-process materials and drug products (21 CFR 211.170) could create problems due to radiation safety concerns. If the radiation safety risks outweigh the quality control benefits, an exception could be proposed to this part of the CGMP regulations. However, another quality control measure that reduced the potential risks to product quality, such as parameter checks of critical processing steps, would have to be present. Once established, this type of quality control measure could potentially fulfill the intent of this part of the CGMP regulations.

Q23: Many PET facilities are synthesizing drugs for both research and clinical use. Is it possible to carry on an active basic research program in a facility that is also producing CGMP drugs in the same facility?

A: Yes.

Q24: At what point during the process should the request for an exemption to CGMP regulations be requested?

A: The request for an exception or alternative can be sent to the FDA at any time after the final rule on CGMPs for PET facilities is published. This request is not a part of the drug application process and will probably be handled by the Office of Compliance. It is expected that such requests will be consistent with the PET center's application

submission.

Q25: If a PET center comprises five hospitals, and we want to manufacture the FDG at one site and distribute it among our five hospitals, are we considered five different manufacturing sites, or is it just distribution among our own departments?

A: This would be considered one manufacturing site.

Q26: The PET activities we are doing fall into the category of physiological research. Do we need a CGMP license? Is there a distinction between registration and applications for CGMP?

A: There are no CGMP licenses or applications. Generally, PET activities require either an IND, NDA, or ANDA (see *Federal Register* notice from February 27, 1995). Activities conducted under any of these applications must be conducted in compliance with applicable CGMP regulations (21 CFR Parts 210 and 211) to ensure product quality for any drug administered to patients.

Q27: If we were to apply for a limited IND, would that automatically put us into this CGMP process?

A: Any facility that manufactures drugs for human use should be using CGMPs. The FDA Guideline on the Preparation of Investigational New Drug Products (Human and Animal) dated March 1991 provides guidance on CGMP requirements for investigational new drug (IND) applications.

Q28: In the guidelines there are three classes of sterile areas. Are there any specific space requirements for each of these particular areas?

A: No. There should be adequately defined space to prevent contamination or mixups to do the job effectively, as described in 21 CFR 211.42.

Q29: Is there a mechanism by which some of you could come and spend some significant amount of time in one or more PET centers and actually see and really understand how we have to work?

A: Yes. Send a letter to the Director, Office of Compliance, HFD-300, 7520 Standish Place, Rockville, Maryland 20855, requesting a visit.

Q30: Is it possible for you to simplify the ANDA process, at least for FDG manufacturing? Can you provide some addresses for applying for ANDAs?

A: We intend to do everything we can to simplify the regulatory processes. The staffs in

the Center for Drug Evaluation and Research (CDER), Office of Generic Drugs (OGD) and Office of Compliance (OC) will be available to help answer questions whenever needed during the application process. All application packages (IND, NDA and ANDA) can be obtained by calling the CDER Drug Information Branch at 301-827-4573. The application contains the mailing addresses for the different Offices.

Q31: How do we handle apparent conflicts between CGMP and Nuclear Regulatory Commission (NRC) regulations with respect to sterile product preparation? The FDA likes to have everything under positive pressure, hepa-filtered coming in. NRC likes to have everything under negative pressure, hepa-filtered going out. How can this conflict be resolved?

A: The section on environmental controls in the draft guidance has been written to address CGMP requirements, and there are ways to proceed according to the guidance that would not conflict with negative pressure requirements. At this time, the FDA is unaware of any other conflicts.

Q32: If an academic institution is registered as a manufacturer and has an approved NDA for a PET radiopharmaceutical, are we free to market and distribute this drug anywhere?

A: Yes, as long as the applicable requirements of the FD&C Act and other Federal laws have been met.

Q33: It seems that the guidelines were written for FDG and then in a few places it says they're applicable to other PET radiopharmaceuticals. We make more radioactive water drug products than any other place, and we are talking about doing the clinical use. If I look at how we make O-15 water, we'd have to ask for an alternative or an exception for virtually every step of the process. Does that mean you would be expecting 20 or 30 different requests for alternatives or exceptions where we have to deviate because these were written for something with a 108 minute half-life?

A: What you are describing was never under consideration in the preparation of the draft guideline. The guideline was written with liquid injectable PET products in mind, using F-18 FDG as an example. Every request for an exception or an alternative should be documented and justified. However, a number of requests can be bundled together in one application.

Q34: If a PET NDA holder contracts with another PET facility to manufacture a PET radiopharmaceutical, is the NDA holder liable for CGMP violations of the contract manufacture?

A: NDA holders (sponsors) are responsible for meeting all application commitments and for ensuring that contract facilities comply with all applicable provisions of the FD&C

Act (Act) and regulations. Because the contract manufacturer is engaged in the manufacture of a drug, it is also responsible for compliance with the Act and regulations. Decisions to initiate FDA enforcement actions are made based on the facts of each particular case.

Q35: If a PET IND holder distributes a PET radiopharmaceutical to another PET facility that fails to comply with the IND regulations (commercial distribution of an investigational new drug), who is liable?

A: IND holders (sponsors) are responsible for, among other things, selecting qualified investigators, ensuring proper monitoring of the investigations and ensuring that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND (see 21 CFR § 312.50).

More specifically, under 21 CFR § 312.56(b), a sponsor who discovers that an investigator is not complying with the signed agreement, the general investigational plan, or the requirements of 21 CFR Part 312 or other applicable regulations, must promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. Investigators are also responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and for the control of drugs under investigation (see 21 CFR § 312.60, 312.61). Decisions to initiate FDA enforcement actions are made based on the facts of each particular case.

Q36: Must ANDA applicants obtain a letter of authorization from ICP for their chemistry DMF, or is the NDA complete as submitted to support the review of an ANDA for F-18 FDG?

A: A Drug Master File (DMF) is a mechanism by which a company can supply information to FDA for review without having to directly give the information to IND or NDA/ANDA applicants. The DMF is maintained at the agency and FDA reviewers can look at the data in the DMF, but the data are not shared with anyone outside of the agency. DMF's provide a mechanism to protect proprietary information. If an applicant wants to use data in a DMF that they do not own, a letter of authorization from the DMF holder must be provided to the applicant and must be submitted with the application to allow FDA access to the DMF data while reviewing the application. A letter of authorization does not give the applicant permission to see the DMF. An ANDA applicant does not need a letter of authorization from the innovator drug sponsor in order to submit an ANDA.

An ANDA applicant has several options when preparing an application for submission. The applicant may:

- Generate and submit all of their own data and information
- Collect and analyze published literature that may supply the needed information.
- Acquire a letter of authorization from the DMF holder if the information provided in the DMF contains data essential to the review and approval for the ANDA.
- Acquire a letter of authorization from another applicant who may have the data in their application.

For example, if a DMF contained information on a particular cyclotron or chemical processing unit that was not available from another source, an ANDA applicant proposing to use that cyclotron and chemical processing unit could obtain a letter of authorization from the DMF holder to reference the DMF. Using information in a DMF may save time and effort of the part of the applicant, but is not required if the information is available from another source.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

April 18, 1997

On March 21, 1995, the Food and Drug Administration (FDA) held a public workshop entitled "Positron Emission Tomography (PET) Regulatory Workshop." During the course of the workshop, many members of the audience asked questions about a variety of issues related to the regulation of PET drug products. On October 24, 1996, the FDA issued the first of a series of answers addressing these questions.

In addition, on October 27, 1996, representatives from the Food and Drug Administration (FDA) participated in the Eighth Annual International PET Conference organized by the Institute for Clinical PET to provide further guidance on the regulation of PET products. A set of questions was presented to the FDA representatives at this workshop.

In an effort to address questions raised at the March 21, 1995, and October 27, 1996, workshops, staff members in the Offices of Generic Drugs, Pharmaceutical Science, Compliance, and Review Management in the Center for Drug Evaluation and Research and staff from the Health Care Finance Administration (HCFA) have developed answers (see attached).

The FDA understands that questions about the regulation of PET products will continue. Therefore, the Agency is undertaking additional efforts to facilitate the dissemination of information on PET drug products to industry and the public. Planned activities include a second public workshop on April 28, 1997, and several guidance documents.

For further information contact:

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Center for Drug Evaluation and Research
5600 Fishers Lane
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(301) 443-0260

April 18, 1997

Guidance for Industry[1]

Pet Questions and Answers

Questions for FDA from March 21, 1995 Workshop

Q1: What will happen when an ANDA is submitted and there is ongoing clinical activity for the drug at that site?

A: Under these circumstances, FDA does not intend to prevent the use in clinical practice unless a safety problem is identified. FDA does not intend to take regulatory action against any PET facility during the preparation and FDA review of an ANDA if the facility demonstrates a good faith effort to comply with FDA regulations by developing a well-designed written plan or procedure with reasonable and defined time frames.

Q2: If we were working under PRC, would we be classified as a drug manufacturer?

A: We would not expect a person who owns or operates a PET facility to register as a drug manufacturer if the facility is only doing PRC work (i.e., limited solely to physiological research) and/or investigational clinical trials, not for sale and is not selling the drug product.

Q3: Are facilities that manufacture PET radiopharmaceuticals for (a) purely physiological research, (b) investigational clinical trials, required to register as a drug manufacturer?

A: Generally, persons who own or operate establishments that manufacture PET radiopharmaceuticals must register with FDA in accordance with section 510 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360, and FDA regulations. However, owners or operators of PET facilities may be exempt under § 207.10(d) if they manufacture PET radiopharmaceuticals solely for use in purely physiological research and/or investigational clinical trials, and not for sale.

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[1]This guidance has been prepared by the PET Steering Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on PET products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and/or regulations.

Q4: Did FDA intend that PET Regulatory Committees (PRC) would have a broader mandate than Radioactive Drug Research Committees (RDRC)? What is the relationship between PRCs and RDRCs?

A: FDA proposed the concept of a PRC in response to requests from the PET community for a committee devoted specifically to PET. As described in the guidance document [60 *FR* 10594], much of the guidance on the operation of a PRC is identical or very similar to the RDRC requirements in 21 CFR 361.1. FDA did not intend that PRCs would have a broader mandate than RDRCs.

FDA is planning to publish a proposed rule amending 21 CFR 361.1 to update and clarify the requirements for radioactive drug products for basic research. If this proposal is finalized, the need for separate PRCs for PET radiopharmaceuticals will be eliminated.

Questions from Institute for Clinical PET October 27, 1996 Workshop

Q5: What triggers a compliance inspection at a PET center between now and when their ANDA is filed?

A: Generally, FDA performs GMP inspections for drug manufacturing facilities every two years and in advance of approvals for NDAs and ANDAs, changes in plant layouts or manufacturing operations or procedures, consumer complaints, reports of adverse reactions, and product recalls. When there are questions or concerns regarding public health or product safety, FDA may inspect any manufacturing facility or institution at any time.

Q6: Does FDA intend to inspect PET center manufacturers using a local compliance inspector or will an "expert" PET inspector be involved?

A: FDA intends to inspect PET center manufacturers using a "team approach," involving local FDA field investigators, personnel from CDER (primarily, a chemist and a manufacturing compliance officer), and other FDA personnel as needed. FDA intends to ensure that people with the necessary expertise are involved in PET inspections.

Q7: In the Memorandum Opinion of the U.S. District Court of the District of Columbia. (Section IV.B.2., page 22) Judge Sullivan states "The FDA has not made a blanket decision to enforce the FD&C Act against all PET manufacturers without exception." What are the criteria FDA will use to decide whether or not to enforce the Act at a specific PET site?

A: FDA has limited enforcement resources and does not intend to initiate an enforcement action against a PET manufacture for minor violations. FDA expects PET manufacturers to voluntarily comply with all applicable requirements. The agency

intends to engage in dialogue with the PET community and to provide appropriate guidance to bring PET manufactures into compliance. In exercising its enforcement discretion, the agency considers a wide range of factors depending on the facts of each individual case. Nonetheless, among the factors likely to be considered in this highly fact-specific endeavor are: (1) the public health significance of the violations and (2) the persistence, as well as the pervasiveness, of the violations observed.

Q8: Since it seems that FDA will selectively enforce the FD&C Act on PET Centers, will distribution throughout a university system (multiple hospitals) be a situation that might prompt an enforcement inspection?

A: Normally, the type of distribution system would not prompt an inspection. However, routine facility inspections are conducted periodically at all facilities. See the response to question 5 above regarding when such inspections are normally conducted.

Q9: Same question, only for a regional distribution outside a university system (i.e., commercial distribution throughout a geographic region, including across state lines).

A: See response to question 8, above.

Q10: Are any areas of CGMP, either implicitly or explicitly, excluded from requests for exemption?

A: No. We will accept properly justified requests for exceptions or alternatives to any CGMP provision.

Q11: In the case of FDG, please clarify the interrelationship between the NDA, DMF (clinical and chemistry) and ANDA.

A: An NDA containing data that established the safety and efficacy of FDG was submitted for premarket approval. Such an application could contain original clinical safety and efficacy data and CMC information or refer to data from other sources such as another NDA or DMF. If an applicant wants to conduct clinical studies of an indication not previously approved, an IND should be submitted to cover the studies for safety and efficacy. Submission of a new NDA or supplement to an already approved NDA or ANDA should then be submitted for approval of the new indication. Any other applicant seeking approval for the FDG product (i.e., same strength, dosage form, indications, and route of administration) may submit an ANDA.

Because an ANDA is based on the determination of safety and efficacy that was established when the agency approved the NDA, no "clinical" data is needed in an ANDA. Therefore, a reference to a DMF containing clinical data would not be necessary.

A DMF may be referenced for certain information that is to be included in the chemistry section of the ANDA. If certain confidential information required for approval cannot be provided by the applicant in the ANDA, a reference to a DMF, supported by a letter of authorization from the holder of the DMF, can be used to supply the information.

Q12: What is the mechanism for applying for CGMP exemptions/alternatives?

A: PET manufacturers applying for CGMP exceptions or alternatives should submit a citizen petition to the Dockets Management Branch, Food and Drug Administration, Department of Health and Human Services, rm. 1-23, 12420 Parklawn Drive, Rockville, MD 20857. The phrase "PET Request for Exception or Alternative" should be clearly marked on both the envelope and the petition. The requirements for a citizen petition, and a template for a petition, are provided at 21 CFR 10.30.

Requests for an exception or alternative may be submitted by individual PET manufacturers, trade associations, or a group, as long as the facts presented are sufficiently individualized for each manufacturer seeking the exemption or alternative. FDA believes it is necessary to review individual requests to determine whether exceptions or alternatives are consistent with the basic principles of the CGMP regulations.

Q13: What information does FDA consider fundamental to a properly prepared request for CGMP exemptions/alternatives?

A: The specific information that should be submitted depends upon the nature of the request. A request for exception or alternative should include the following: (1) an explanation, with supporting data as necessary, of why compliance with a particular part of the CGMP regulations is unnecessary or cannot be achieved; (2) a description, with supporting data as necessary, of alternate procedures or controls that satisfy the purpose of the CGMP requirement; (3) other information justifying an exception or alternative. Relevant supporting information might include the radiological risks to personnel or patients, the manufacturing characteristics of the PET center, such as size, scale or capacity of equipment, number of lots per day and number of containers per lot, number of personnel, and the characteristics of the product including its packaging.

Q14: Under what conditions will clinical indication supplements allow other ANDA holders to include the new indications?

A: An ANDA for a product contains all of the indications approved in the NDA for the product unless covered by exclusivity. New indications may be afforded market exclusivity for a period of three years if clinical studies were essential to approval of the new indication. During the period of exclusivity, no other application holder

would be permitted to include this indication in its labeling, unless they conducted full safety and efficacy studies for the desired indication. Once exclusivity, if any, expires, ANDA holders should submit labeling supplements to change their labeling to match that approved in the NDA.

Q15: What activities (i.e., in-house use, regional distribution) might be allowed during the preparation of an ANDA, facility development, and procedure validation?

A: Refer to the answer to question 1.

Q16: Would a PET manufacturer be required to monitor and/or enforce any element of "off-label" use by prescribing physicians?

A: Although PET manufacturers are prohibited from directly or indirectly promoting any off-label use, they do not have an affirmative obligation to monitor or prohibit off-label use by prescribing physicians. However, each applicant having an approved NDA or ANDA is required to report adverse drug experiences obtained or received from any source (21 CFR 314.80), including adverse reactions to off-label uses of the drug. In addition, with regard to studies of off-label uses of its approved products, the applicant is required to include in its annual report to FDA any published clinical trials on "new uses." 21 CFR 314.81(b)(2)(vi).

Q17: Please clarify a physician's authority to prescribe off-label uses of approved drugs. Do you need to file an IND for such uses?

A: FDA's policy on "off-label" use of marketed drugs and biologics has been stated by the Office of the Associate Commissioner for Health Affairs. In the FDA's Information Sheets for Institutional Review Boards and Clinical Investigators, on Page 61, it states the following:

"Good medical practice and patient interest require that physicians use commercially available drugs, and biologics according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a product in this manner as part of the 'practice of medicine' does not require the submission of an Investigational New Drug Application (IND) or review by an Institutional Review Board (IRB), unless such review is required by the institution at which the product will be used."

"FDA encourages the submission of applications containing the relevant safety and effectiveness information on drugs and biologics being prescribed for 'off-label' uses. The Agency believes that it is important for appropriate uses to become part of the

approved labeling so that patients may benefit from reliable and up-to-date information about the safe and effective uses of such drugs and biologics."

Furthermore, regarding investigational use of marketed drugs and biologics, the policy states:

"Investigational use" suggests the use of an approved product in the context of a clinical study protocol [see 21 CFR 312.3(b)]. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND is generally required. According to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug, however, does not require an IND if:

(1) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

(2) it is not intended to support a significant change in the advertising for the product;

(3) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(4) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and

(5) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR part 312.7].

For additional information on whether or not an IND is required in a specific situation, contact:

Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
(301) 443-5818

The FDA's Information Sheets for Institutional Review Boards and Clinical Investigators from the Office of the Associate Commissioner for Health Affairs can be

found on the World Wide Web: http://www.fda.gov/oc/oha/toc.html.

Q18: Can diagnostic agents (radiopharmaceuticals) be placed on a "fast track" for approval such as therapeutic agents? How could we make this happen?

A: The Center for Drug Evaluation and Research, Manual of Policies and Procedures (MAPP 6020.3), *Priority Review Policy*, April 22, 1996, describes the Center's priority review policy. Accordingly, an NDA receives priority review when "the drug product, if approved, would be a significant improvement compared to the marketed products (including non-"drug" products) in the treatment, diagnosis, or prevention of a disease." Generally, ANDAs are not significant improvements compared with marketed products, therefore, they would not be placed on a "fast track" review process. This policy also describes how this significant improvement may be demonstrated.

Q19: How does the FDA view the association of a PET center with a commercial partner for marketing and distribution? Is it a positive or negative factor?

A: FDA has no position on commercial marketing arrangements between application holders and distributors.

Q20: Please clarify whether percent yields of FDG below the established action limit are cause for batch rejection.

A: The drug product may be released if all the established release specifications are met (radiochemical purity, chemical purity, etc). Action limits are not batch release criteria. Action limits for percent yield are established in the master production record for a particular set of conditions for the manufacture of a drug product. At the conclusion of manufacturing of each lot, theoretical and actual yields are compared. If the actual percent yield falls outside the specified upper or lower ranges, an investigation should be conducted to identify the possible cause(s). The investigation should be documented in writing in a "manufacturing deviation report."

For example, a PET Center establishes specified upper and lower acceptable "percent yields" at 85% to 35% for the production of [^{18}F]FDG. The product's acceptability and conformance to approval criteria between these percentages have been documented and the method of production validated. Following production of a batch of [^{18}F]FDG, the yield percentage is calculated accurately at 29.7% (outside the acceptable range of "percent yields").

Release content testing (e.g., radiochemical purity, radiochemical identity, specific activity, total activity, radionuclidic purity, radionuclidic identity, chemical purity, and pH) as specified for the conditions of release for this lot of [^{18}F]FDG may be conducted

and even completed.

Q21: Please clarify whether batch volumes of FDG below the established action limit are cause for batch rejection.

A: Volume is not a release criteria. See response above.

Q22: Please clarify if HPLC is required as a final product quality control of FDG.

A: HPLC is not required for final product quality control. However, suitable validated analytical methods to monitor the identity, quality, purity, and strength of the drug product should be conducted.

Q23: For ANDA applicants, please clarify whether critical raw materials from different suppliers must be qualified through complete stability studies. How many runs are necessary.

A: For applicants submitting an ANDA with multiple suppliers:

(a) for the starting materials, oxygen-18 enriched water, fluorine-18, and mannose triflate, information related to one batch using the material from each supplier including a stability study, should be submitted in the application. In addition, a Certificate of Analysis (CoA) from the supplier and your own CoA (tests and specifications) should be provided.

(b) of raw materials, inactive components, reagents and/or solvents should provide each supplier's CoA, and the name and address of the supplier.

For applicants with an approved ANDA, who want to change a supplier:

(a) for a starting material, information related to one batch using the material from the new supplier, including a stability study should be submitted in a prior approval supplement.

(b) of raw materials, inactive components, reagents and/or solvents, should submit the supplier's CoA, and the name and address of the new supplier in the annual report.

Q24: For ANDA applicants, please clarify whether different batch sizes must be qualified through complete stability studies. How many runs are necessary?

A: For approval of an ANDA, chemistry, manufacturing, and controls data, including stability data, from one batch should be submitted. ANDA holders should maintain

documentation from three validation batches postapproval. A batch is defined as one production run (see question 26 for further definition). Where a 60 minute irradiation time is employed, a single stability batch will suffice. Where a range of irradiation times are employed, three additional batches of the drug product manufactured at the upper end should be studied.

Q25: Regarding other PET tracers (i.e., C-11, N-13, O-15, F-18) --

a. How do you envision bringing them into the regulatory stream?

b. A realistic estimate of time for extending the regulatory umbrella?

c. Any acknowledgment for the comparatively limited utility of such products?

A: a. Use of PET radiopharmaceuticals should be through the RDRC, IND, NDA, or ANDA process.

b. FDA had requested that the manufacturers of PET radioactive drugs comply with the law and expects an earnest effort from PET manufacturers to comply with the Federal Food, Drug, and Cosmetic Act to avoid any compliance action.

c. We acknowledge the limited utility of short lived PET radioisotopes (i.e., C-11, N-13, O-15, and F-18) as part of PET radiopharmaceuticals, however, these drugs should still meet safety and efficacy requirements.

Q26: Please clarify the FDA's perspective of what constitutes a batch of a PET radiopharmaceutical, especially with regard to those containing the shorter-lived nuclides 0-15 and N-13.

A: 21 CFR 210.3(b)(2) defines a "batch" as "a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits and is produced according to a single manufacturing order during the same cycle of manufacture." Therefore, in the case of PET radiopharmaceuticals, the material produced during a single irradiation cycle using the same synthesis and/or purification operation would constitute a batch.

Q27: How does the PET RDC fit within the scope of FDA's plans to regulate PET agents?

A: FDA is considering proposing changes to the regulations affecting all research with radioactive drugs conducted under an RDRC. Under these proposed changes, the need for a separate PRC for research with PET radiopharmaceuticals would be eliminated.

Q28: To what extent is FDA prepared to receive IND applications for other PET radiopharmaceutical (O-15 water, N-13, ammonia, F-18 fluoroDOPA, C-11 methionine, etc.)?

A: FDA is fully prepared to review the drug applications submitted by the sponsors.

Q29: If a PET facility (that currently produces FDG under an IND) wants to expand the indications for FDG what are the requirements to demonstrate equivalence between the FDG produced by the IND holder and that produced under the NDA?

A: Adequate and well controlled studies demonstrating the safety and effectiveness of the drug should be conducted and submitted for approval of any new indication

Q30: Given the varying production quantities of FDG (in mCi), does FDA intend to limit the distribution of the product only to either the final product container or unit-dose containers?

A: Under 21 CFR § 314.93(b), if the strength of a drug product submitted for approval under an abbreviated new drug application (ANDA) differs from the approved strength of the reference listed drug (RLD), it is necessary to file a suitability petition before filing the ANDA. See 21 CFR § 314.93(c). Generally, a change in the concentration or total volume of a parenteral drug product will constitute a change in strength. The labeling for the RLD for Fludeoxyglucose F18 ([^{18}F]FDG) Injection designates a total volume of 16 $\pm$ 3 mL of isotonic saline (plus the requisite amount of [^{18}F]FDG. Therefore, an [^{18}F]FDG drug product submitted for approval under an ANDA should indicate the same total volume specified by the RLD labeling (13 - 19 mL), unless a suitability petition has been approved addressing the change in total volume (i.e., strength).

Q31: Could you describe the role of the PET Research Committee in physiologic research studies? Specifically, please discuss the issues regarding studies where injection in a human has not yet occurred. Is the issue pharmacologic effect? Also, what about compounds that have been used in humans without difficulty and are only minimally modified (a chemical analog) with no change in pharmacologic potency?

A: See response to question 27 regarding the role of PET Research Committees.

Q32: The USP has monographs for many PET tracers (about 8 or 9). Do these have any application in the FDA process?

A: Under section 501(b) the Federal Food, Drug, and Cosmetic Act, unless FDA adopts alternative standards, the USP monographs contain the standards for identity, strength, quality, and purity the drug products for which monographs are available. NDA or ANDA applicants for products covered by USP monographs should demonstrate in their applications that their products meet these standards.

Q33: Assuming that new indications for FDG require an IND, would the FDA consider allowing reasonable patient charges for the cost of the drug/imaging procedure (this is generally denied). In other words, is it possible to charge for investigational studies

under an IND? If so, how does one go about this?

A: Under FDA regulations, 21 CFR 312.7, the investigator may request permission to charge for the drug supplied in the investigational studies. A letter requesting permission with a detailed explanation of the reason why it is necessary to charge would be sent to the review division.

Q34: I understand that CGMP's apply to the production of any drug for human use, regardless of whether the drug is produced under IRB, RDRC (PDRC), IND, ANDA, or NDA. I also understand that production facilities operating under ANDAs and NDAs are legally required to undergo periodic CGMP inspections (every two years?). I further understand that any facility is subject to a CGMP inspection in the event of questions related to public health and safety. First, is my understanding of these issues correct? If so, do legal requirements exist for the periodic CGMP inspection of production facilities operating under IRB, RDRC (PDRC), or IND? If there are no legal requirements, how often is a production facility operating under IRB, RDRC (PDRC) or IND inspected for compliance with CGMP?

A: The CGMP regulations (21 CFR Parts 210 and 211) contain the minimum standards for preparation of drug products for administration to humans. CGMP inspections for manufacturing facilities are based on preapprovals for NDA/ANDA, changes in plant layouts, or in manufacturing operations or procedures, consumer complaints, reports of adverse reactions, and product recalls.

Currently, FDA performs preapproval CGMP inspections for the submission of NDAs and ANDAs and generally, routine CGMP inspections are performed every two years after final approval. Any facility that manufactures drugs for human use should be in compliance with the CGMP regulations. The FDA Guideline on the Preparation of Investigational New Drug Products (Human and Animal) dated March 1991 provides guidance on CGMP requirements for investigational new drug (IND) applications. CGMP inspections for IND applications are conducted on about one percent of all applications. Generally, these inspections are "for cause" due to potential problems or concerns regarding product safety. Any drug manufacturing facility is subject to a CGMP inspection in the event of questions related to public health and safety.

Manufacturing practices and standards for radioactive drugs for certain research uses, under 21 CFR Part 361.1, are evaluated during FDA inspections of an institution's RDRC.

Q35: Do good laboratory practices (GLPs) pertain only to animal pharmacology studies, or are GLPs also relevant to other areas (e.g., quality control procedures on the final drug product)? To me as a chemist, "laboratory" means a chemical research area, a production area, or a QC testing area. Do GLPs apply to these areas?

A: Good Laboratory Practice for Nonclinical Laboratory Studies, 21 CFR Part 58, is intended to assure the quality and integrity of safety data for certain animal studies. CGMP regulations, as described in 21 CFR Parts 210 and 211, pertain to the preparation of drug products for administration to humans or animals. If chemical research areas, production areas, or QC testing areas participate in the preparation of drug products for administration to humans or animals, then these areas and their activities should operate in compliance with CGMP regulations.

Q36: To alleviate confusion between the FDA and the PET community, should ANDA applicants withhold submission of their applications until after the recently announced 1997 FDA workshop? What guidance can you provide applicants who have already filed ANDAs with OGD?

A: No. FDA has announced on several occasions that it is ready to receive ANDAs. As stated at the recent ICP meeting, FDA is developing a guidance document for the submission of ANDAs, with particular information for Fluorodeoxyglucose - F18 Injection, that should assist applicants who are preparing ANDAs for submission to FDA. If an application has already been submitted to OGD, it will be reviewed but can be amended to correct deficiencies.

Q37: Let's assume that an analytical method has been validated in an NDA. If an ANDA applicant uses the same analytical method as in the NDA, must the methods validation be repeated, or are system suitability tests (replicate injections, peak tailing, theoretical plates) sufficient? If an ANDA applicant uses a USP compendial analytical method, must the methods validation be repeated, or are system suitability tests (replicate injections, peak tailing, theoretical plates, etc.) sufficient? What changes to a method (supplier or equipment, detector, flow rates, solvents, supplier of standards, etc.) necessitate a revalidation of the method?

A: If the applicant is using a USP method, system suitability data are acceptable, per USP <1275> and methods validation data would not be required.

If the applicant is not using a USP method, the applicant must provide methods validation data to support approval of its ANDA (21 CFR 314.50(d)(1)(ii)(*a*)), although the methods validation data may be provided by reference to data in an NDA if the NDA holder authorizes the ANDA sponsor to rely on its validation data for submission in the ANDA. If any changes are made to the approved analytical methods, the revised method should be revalidated.

Questions for HCFA from March 21, 1995, Workshop

Q38: Why should radiopharmaceuticals be the only drugs that get approved by the FDA but then have to go through an additional level of review of Medicare coverage for the

indicated uses, for labeled uses?

A: The one difference here is that this is a drug for diagnostic purposes rather than therapeutic, it is used in combination with a diagnostic technology and competes with a variety of diagnostic technologies that may or may not provide similar imaging.

From HCFA's point of view, PET scanning involves the use of both a device and a drug as a diagnostic tool. We are interested in whether something is safe, whether it does what it is supposed to do, and how well it does what it is supposed to do. How does it compare with other alternatives? What are the appropriate uses? And if we can find out, if we have the information available to us and the analytical capability, what is the relative cost effectiveness compared to the alternatives?

Q39: Recognizing that private insurers and CHAMPUS have agreed to reimburse for PET, what can you say that you could do in the context of the promotion of the public health for the Medicare population and the population in general, as well as the protection of the public health?

A: We consider it a responsibility to assure our beneficiaries appropriate and effective health care. We now see the value of being able to move more quickly even if not with global decision, to make coverage decisions more quickly, to get ahead of the technology assessment curve and to be able to make coverage decisions more quickly even at a limited basis and then expand them as we get more information.

Q40: As well as demonstrating that PET is safe and clinically effective, if promoted, it could be proven to be cost-effective. What are you doing in the promotion part? We suggest an interim reimbursement policy to allow us to demonstrate that PET is truly not only safe through the FDA route, but also is cost-effective.

A: Using axillary lymph node imaging as an example, is the data robust enough to base a decision on -- a decision that will affect a population as large as the American female population with breast cancer? Is a study of 50 patients sufficient to promote the indication? Well-planned clinical trials can help answer the questions of safety and efficacy. The agencies have learned a lot during the PET evaluation process. HCFA might be able to start planning approvals after FDA approval for limited sites to start using the technology and return data to us and FDA and AHCPR to see if broader coverage is warranted.

Q41: Following FDA approval of a drug, could individual carriers make decisions for coverage as an interim policy?

A: It is undecided at this point whether an interim policy could be instituted. It will have to be discussed internally.

Q42: FDA approval of an NDA is necessary but not sufficient grounds for HCFA approval. Does that mean that a study conducted under and IND would never be eligible for HCFA approval?

A: Correct, IND studies and off-label indications would not be approved by HCFA.

Q43: Would a drug that has an NDA approval, but is being used for off label indications be approved for reimbursement by HCFA?

A: The reimbursement for off-label uses of a drug can be left to individual carriers to decide, and their policies may differ. HCFA could make a decision for national coverage policy if it considered by HCFA to be needed at the time.

FDA PET WORKSHOP
APRIL 28, 1997

SLIDE PRESENTATIONS

FILING REQUIREMENTS FOR ABBREVIATED NEW DRUG APPLICATIONS (ANDAs) FOR POSITRON EMISSION TOMOGRAPHY (PET) DRUG PRODUCTS

With specific information for ANDAs submitted for Fludeoxyglucose F18 Injection

PETER RICKMAN,
OFFICE OF GENERIC DRUGS

APRIL 28, 1997
PET PRODUCTS WORKSHOP

CONTACT POINT: ALL INQUIRIES

PETER RICKMAN (301)594-0315

MAIL EVERYTHING TO:

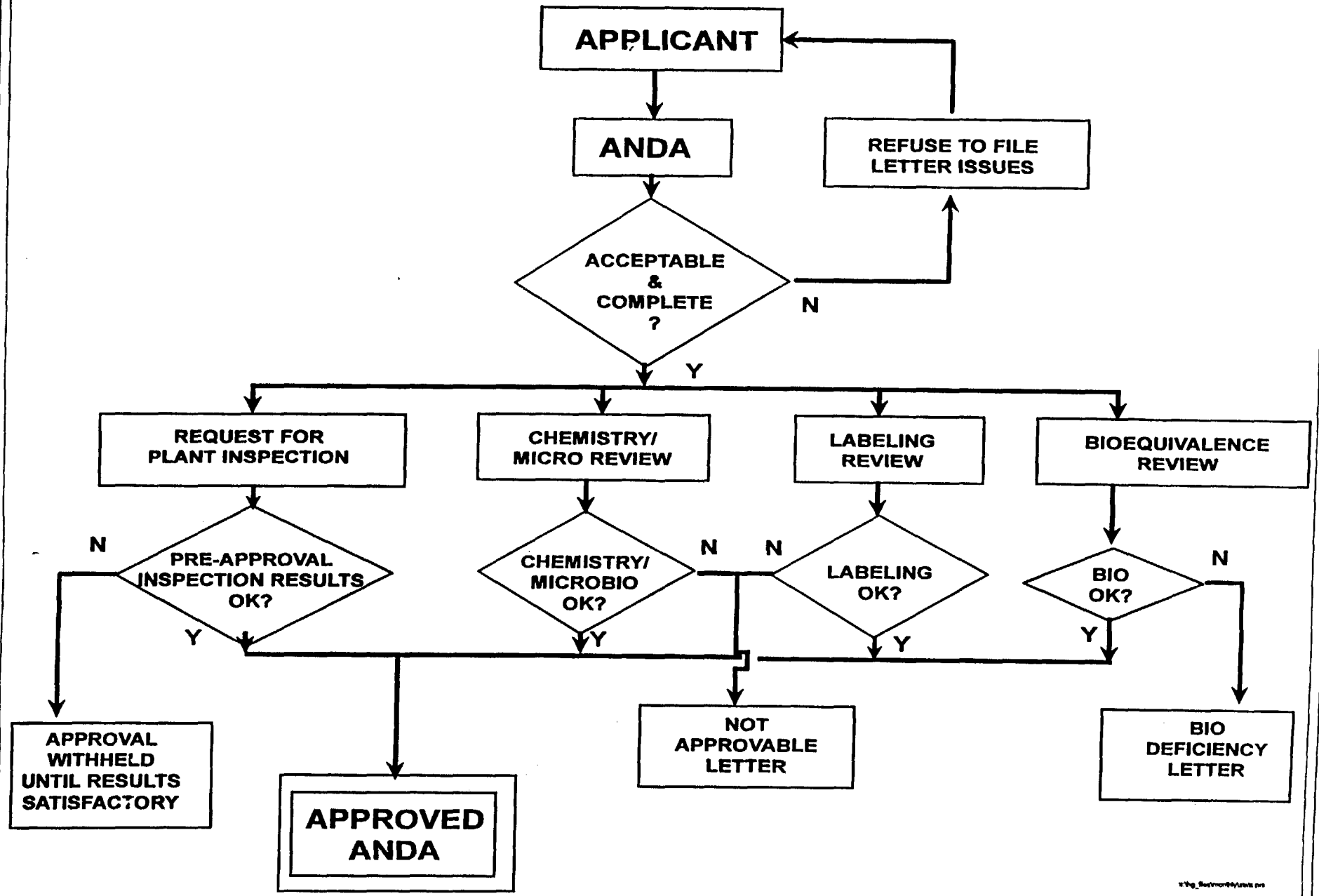
OFFICE OF GENERIC DRUGS
CDER, FDA
METRO PARK NORTH II
7500 STANDISH PLACE
ROCKVILLE, MD 20857-2773

ANDA ELIGIBILITY

Same as a Listed Drug [21 CFR 314.92]

- IDENTICAL ACTIVE AND INACTIVE INGREDIENT(S)
- DOSAGE FORM
- STRENGTH
- ROUTE OF ADMINISTRATION
- CONDITIONS OF USE

GENERIC DRUGS REVIEW PROCESS



APPLICATION INFORMATION [21 CFR 314.94]

Three Copies

- **Archival Copy (original) BLUE**
- **Review Copy (duplicate) RED/ORANGE**

  Bio data (duplicate) in ORANGE copy

- **Field Copy**

COVER LETTER

Signed and Dated

Brief Introductory Statement

Purpose of the Submission

Type of Submission:

- ***Original**
- ***Amendment\Supplement**
- ***Annual Report**

- **Debarment Certification/List of Convictions**

  Use of a debarred individual/ firm within the meaning of 21 U.S.C. 335a, may preclude the approval of the application

The application should contain:

a debarment certification

a convictions statement

- **Field Copy Certification**

  Applicant should submit a certification that indicates that an true third copy of the technical sections (chemistry, manufacturing and controls) has been submitted to the appropriate FDA district office.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314).*

NAME OF APPLICANT
Applicant

DATE OF SUBMISSION
April 28, 1997

ADDRESS *(Number, Street, City, State and Zip Code)*
100 Main Street
Anywhere, USA 00000

TELEPHONE NO. *(Include Area Code)*
(301) 594-0315

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
Fludeoxyglucose F 18 Injection

PROPRIETARY NAME *(If any)*
None

CODE NAME *(If any)*
None

CHEMICAL NAME
2 - deoxy - 2 - [F-18] fluoro - D - glucose

DOSAGE FORM
Solution

ROUTE OF ADMINISTRATION
Intravenous

STRENGTH(S)
6.8 - 35.7 mCi/mL

PROPOSED INDICATIONS FOR USE

Fludeoxyglucose F18 Injection is indicated for the identification of regional abnormal glucose metabolism associated with foci of epileptic seizures.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, **NEW DRUG OR ANTIBIOTIC APPLICATIONS** *(21 CFR Part 314)*, **AND DRUG MASTER FILES** *(21 CFR 314.420)* **REFERRED TO IN THIS APPLICATION:**

DMF references (if applicable)

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG
Fludeoxyglucose F18 Injection

HOLDER OF APPROVED APPLICATION
Downstate Clinical PET Center

TYPE SUBMISSION *(Check one)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☒ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION *(e.g., Part 314.70(b)(2)(iv))* _____

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

X	1. Index
X	2. Summary (21 CFR 314.50 (c))
X	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
X	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
X	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
X	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO. *(Include Area Code)*

WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec.1001.)

TABLE OF CONTENTS

The purpose of the "Table of Contents" is to help the reviewer locate information in the application.

Each section of the application should be delineated by dividers and tabbed.

Follow the guidance "*Content and Format of an Abbreviated Application*"

BASIS FOR ABBREVIATED NEW DRUG APPLICATION SUBMISSION

NDA 20-306

Fludeoxyglucose F 18 Injection, held by Downstate Clinical PET Center is the applicable reference listed drug (RLD)

The ANDA product must have the same active ingredient, inactive ingredient(s) (except antioxidant, buffer, and preservative), dosage form, strength and route of administration as the reference listed drug product.

PATENT CERTIFICATION AND EXCLUSIVITY STATEMENT

PATENT CERTIFICATION

For: Fludeoxyglucose F18 Injection:

In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the listed drug referred to in this application or that claim a use of the listed drug.

EXCLUSIVITY STATEMENT [314.94(a)(3)(ii)].

A statement addressing exclusivity should be submitted even if no exclusivity exists.

For: Fludeoxyglucose F18 Injection: According to the publication, Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) the reference listed drug is not entitled to a period of marketing exclusivity.

The applicant should provide a statement that the conditions of use, active ingredient, route of administration, dosage form and strength of the proposed drug product are the same as those of the reference listed drug

COMPARISON BETWEEN GENERIC DRUG AND REFERENCE LISTED DRUG

1. **CONDITIONS OF USE** prescribed, reccommended, or suggested in the labeling of the generic have been approved for the RLD;

2. **ACTIVE INGREDIENT**

3. **ROUTE OF ADMINISTRATION, DOSAGE FORM AND STRENGTH**

	Generic Drug Product	Downstate Clinical PET Center
Conditions of use:	**FDG injection is indicated in PET for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.**	**FDG injection is indicated in PET for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.**
Active ingredient:	**Fludeoxyglucose F 18**	**Fludeoxyglucose F 18**
Route of Administration:	**Parenteral**	**Parenteral**
Dosage form:	**Solution**	**Solution**
Strength:	**Specific concentration 6.8-35.7 mCi/mL**	**Specific concentration 6.8-35.7 mCi/mL**

LABELING [21 CFR 314.94(a)(8)]

Refer to the labeling guidance for Fludeoxyglucose F18 Injection.

A side by side comparison of:
container labels, and package insert labeling

All labeling differences between RLD and generic should be annotated and explained.

Four copies of draft or 12 copies of final printed labeling.

BIOEQUIVALENCE: [21 CFR 320.22]

FDG is a parenteral solution intended solely for administration by injection, contains the same active and inactive ingredients as a drug product that is the subject of an approved full new drug application.

A waiver of evidence of in vivo bioequivalence may be requested for Fludeoxyglucose F 18 Injection per 21 CFR 314.22(b)(1)(i).

BIOEQUIVALENCE (CONT)

Provide a side-by-side comparison of the formulation of your proposed drug product with that of the reference listed drug product:

qualitative and quantitative

(active and inactive ingredients)

Inactive ingredients:

Parenteral drug products may only differ from the RLD in inactive ingredients used as a preservative, buffer, or antioxidant.

COMPONENTS AND COMPOSITION

The components and composition of the formulation including the unit composition should be included.

In this section, components (active and inactive ingredients) and composition of the drug product should be listed.

CHEMISTRY, MANUFACTURING AND CONTROLS SECTION

CERTIFICATE OF ANALYSIS (COA)

- Supplier's COA for all components listed in the batch formula used in the manufacture of the drug product

Name and full address of supplier(s)

CHEMISTRY, MANUFACTURING AND CONTROLS SECTION (cont)

- Master production batch record for the largest proposed batch size intended for production

- Completed batch record for the executed batch (batch used to support the approval of the ANDA)

CHEMISTRY, MANUFACTURING AND CONTROLS SECTION (cont)

CERTIFICATION OF COMPLIANCE WITH CURRENT GOOD MANUFACTURING PRACTICES (CGMPs)

- A statement of certification that the manufacturing facility is in compliance with CGMPs

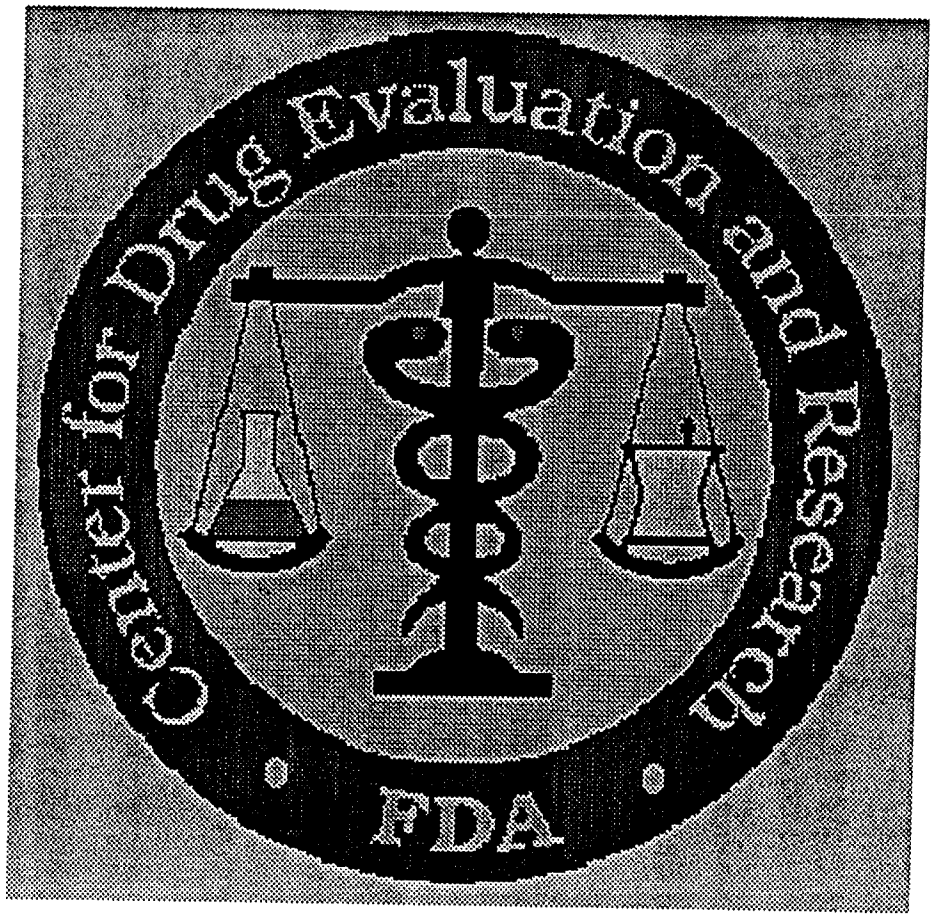
- Provide for applicant and any contract facilities

ENVIRONMENTAL IMPACT ANALYSIS

- Request a categorical exclusion from the preparation of an environmental assessment per 21 CFR 25.24(c)(1)

- Certification of compliance with the federal, state and local environmental laws (signed)

DRUG REGISTRATION AND LISTING SYSTEM



APR 28, 1997

1

2 ## DRLS INFORMATION

FOOD AND DRUG ADMINISTRATION
CDER/OM/DDM/PIMB HFD-095
5600 FISHERS LN
ROCKVILLE, MD 20857

PHONE: 301-594-1086
FAX: 301-594-1122
DRUGLISTING@CDER.FDA.GOV

3 ## IMPORTANT DEFINITIONS (21 CFR 207.3)

- ✓ COMMERCIAL DISTRIBUTION: MEANS ANY DISTRIBUTION OF A HUMAN DRUG. EXCLUDES INVESTIGATIONAL USE AND CARRIERS.
- ✓ ESTABLISHMENT: MEANS A PLACE OF BUSINESS UNDER ONE MANAGEMENT AT ONE GENERAL PHYSICAL LOCATION.
- ✓ MANUFACTURING OR PROCESSING: MEANS MANUFACTURE, PREPARATION, PROPAGATION, COMPOUNDING, OR PROCESSING OF DRUGS. INCLUDES REPACKAGING OR OTHERWISE CHANGING THE CONTAINER.

4 ## REGISTRATION

- ✓ WHO - MANUFACTURERS, REPACKERS, AND LABELERS MUST REGISTER. DISTRIBUTORS AND FOREIGN FIRMS MUST OBTAIN A LABELER CODE. (21 CFR 207.20)
- ✓ ANNUAL REGISTRATION - REQUIRED ACCORDING TO PUBLISHED SCHEDULE. HAVE 30 DAYS FROM RECEIPT OF FORM FDA-2656E TO RETURN TO FDA. (21 CFR 207.21)

5 ## PRODUCT LISTINGS

- ✓ WHO - MANUFACTURERS, REPACKERS, LABELERS, AND FOREIGN FIRMS MUST LIST THEIR PRODUCTS. DISTRIBUTORS CAN DO THEIR OWN LISTINGS OR LET MANUFACTURERS DO IT FOR THEM. (21 CFR 207.20)
- ✓ WHEN - IT IS REQUESTED PRODUCTS BE LISTED OR UPDATED (FORM FDA-2657) AS SOON AS POSSIBLE. REQUIRED UPDATES EVERY JUNE AND DECEMBER.
- ✓ ANNUAL LISTING - FDA SENDS FIRMS COMPLIANCE VERIFICATION REPORT (CVR) EVERY JUNE. ESTABLISHMENT HAS 30 DAYS TO CORRECT AND RETURN TO FDA. FULFILLS JUNE UPDATE.

6 ## DISTRIBUTORS

- ✓ NOT REQUIRED TO "REGISTER" BUT MUST HAVE A LABELER CODE. OBTAINED BY FILLING OUT REGISTRATION FORM (FDA-2656).
- ✓ DISTRIBUTORS CAN CHOOSE TO SUBMIT THEIR OWN PRODUCT LISTINGS TO FDA BY SIGNING BLOCK 14 OF FDA-2656.
- ✓ OTHERWISE, IT IS MANUFACTURER'S (OR REPACKER'S OR LABELER'S) RESPONSIBILITY TO LIST DISTRIBUTORS FOR EACH PRODUCT (FORM FDA-2658).

7 ## NDC NUMBER (21 CFR 207.35)

- ✓ NDC = NATIONAL DRUG CODE
- ✓ LABELER CODE - ASSIGNED BY FDA; UNIQUE TO COMPANY (I.E. ONE OR MORE SITES).
- ✓ PRODUCT CODE - ASSIGNED BY COMPANY; UNIQUE TO PRODUCT'S FORMULATION (I.E. LIST OF INGREDIENTS, DOSEFORM, ROUTE, ETC).

✓ PACKAGE CODE - ASSIGNED BY COMPANY; UNIQUE TO EACH PACKAGE SIZE WITHIN EACH PRODUCT CODE.

8 ☐ NDC NUMBER (CONT'D)

✓ DIFFERENT CONFIGURATIONS:

- THE 5-4-1 CONFIGURATION (12345-1234-1) ALLOWS FOR MANY PRODUCTS WITH A MAX 10 PACKAGE SIZES EACH
- THE 5-3-2 CONFIGURATION (12345-123-12) ALLOWS FOR FEWER PRODUCTS BUT MANY MORE PACKAGE SIZES FOR EACH PRODUCT

✓ PRINTING NDC ON LABEL IS OPTIONAL BUT MUST FOLLOW CERTAIN RULES IF IT APPEARS ON LABEL.

✓ IF NDC IS DISCONTINUED, CANNOT REUSE LABELER OR PRODUCT CODE FOR 5 YEARS.

9 ☐ ALWAYS READ THE SMALL PRINT

REGISTRATION OF A DRUG ESTABLISHMENT OR ASSIGNMENT OF NDC DOES NOT IN ANY WAY DENOTE APPROVAL OF THE FIRM OR ITS PRODUCTS.

10 ☐

Chemistry, Manufacturing, and Controls

Eric Sheinin, Ph.D.

DEFINITIONS

- Drug substance -
  - Fludeoxyglucose F18
- Drug product -
  - Fludeoxyglucose F18 injection

COMPONENTS AND COMPOSTION

- Active - Fludeoxyglucose F18
- Inactive - Saline

RAW MATERIALS CONTROLS

- Name and address of supplier
- Purification
- Specifications and analytical test methods
  - Validate suppliers' results
  - COA
- Retest schedule
- Statement of quality

REFERENCE STANDARD

- Source
- Name and address of supplier
- Proof of identity
  - COA or representative data

MANUFACTURING / CONTRACT FACILITIES

- Name and address
  - including building and room number
  - function of each facility
- Registration number
- Certification of CGMP status

MANUFACTURE OF DRUG SUBSTANCE

- Batch formula
  - list of all ingredients
  - amount of each ingredient

PRODUCTION OF RADIONUCLIDE

- Particle accelerator
  - brief description
  - make and model
- Validation information
  - available on site

OPERATING PARAMETERS

Examples

- Particle energy (max)
- Beam current
- Bombardment time
- Range of values

TARGET BODY

- Description
- Composition
- Foil materials
- Volume
- Establish equivalency for replacement

RECYCLING OF O-18 ENRICHED WATER

- If not recycled, state
- If recycled, give procedures used
  - product quality impurity profile

DRUG SUBSTANCE SYNTHESIS EQUIPMENT

- Flow diagram
- Description and function
- Suppliers
- Procedures for assembly

DRUG SUBSTANCES SYNTHESIS OPERATIONS

- Computer or manual control
- Within established limits
- Step-wise description
- F18 yield

DRUG PRODUCT OPERATIONS

- Procedures
- Reprocessing
- In-process controls
- Blank and executed batch record

IN-PROCESS CONTROL

- Description
- Examples
  - yield of fluoride ions
  - temperature of the reaction vessel
  - gas pressure
  - flow rate
  - synthesis time

SAMPLE EXECUTED BATCH RECORD

- Each component and drug product
  - specifications
  - test procedures
- Names and addresses of all facilities
- Container closure system
  - name and address of supplier
- Results of any tests

LABELING PROCEDURES

- Procedure for labeling of the drug product

CONTAINER / CLOSURE

- Name and address of manufacturer
- DMF reference with LOA
- Glass type
- Closure composition
- Container / closure compatibility
- Acceptance specifications

QUALITY CONTROLS

- Sampling procedures
  - one vial
    - volume withdrawn
    - distribution for testing

SPECIFICATIONS AND ANALYTICAL METHODS

- Appearance
- Identity testing
  - radionuclidic identity
  - radiochemical identity
- Assay (mCi / mL)
- Specific activity

SPECIFICATIONS AND ANALYTICAL METHODS (cont'd)

- Purity testing
  - radiochemical purity
  - stereoisomeric purity
  - radionuclidic purity
  - chemical purity

SPECIFICATIONS AND ANALYTICAL METHODS (cont'd)

- Pharmaceutical quality
  - pH
  - osmolality
  - membrane filter integrity test
  - LAL
  - sterility

METHOD VALIDATION

- Non-USP methods only
- Samples

STABILITY

- For 60 minute bombardment
  - data at expiry
  - single batch
- Additional bombardment times
  - data from 3 batches
  - propose expiration dating

STABILITY (CONT'D)

- Full testing at release and expiry
- Storage conditions
  - inverted position
  - room temperature
- Analytical results on stability batch
- Post-approval stability protocol
  - one production batch per year

FDA WORKSHOP ON SUBMISSION OF ABBREVIATED NEW DRUG APPLICATIONS

Current Good Manufacturing Practices for Positron Emission Tomographic (PET) Radiopharmaceutical Drug Products

Rockville, Maryland
April 28, 1997

1 FDA WORKSHOP ON SUBMISSION OF ABBREVIATED NEW DRUG APPLICATIONS

Current Good Manufacturing Practices for Positron Emission Tomographic (PET) Radiopharmaceutical Drug Products

Rockville, Maryland
April 28, 1997

2 CDR R. K. Leedham, Jr., R.Ph., M.S., BCNP
United States Public Health Service
Division of Scientific Investigations (HFD-343)
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
7520 Standish Place
Rockville, MD 20855
Phone 301-594-1026
Fax 301-594-1204

3 Characteristics of Current Good Manufacturing Practices (CGMPs) for Drugs

- Contain broad objectives
- Minimize "how to" specifics
- Flexible
- Allow new technologies

4 Current Good Manufacturing Practices (CGMPs)

Quality must be built into, rather than tested into, the product

5 Current Good Manufacturing Practices (CGMPs)

Ten Basic Principles

6 Current Good Manufacturing Practices (CGMPs)

1. Assurance that personnel are capable and qualified to performed assigned duties.

2. Assurances that ingredients used in manufacturing have their purported, expected qualities.

3. Process validation to ensure that procedures used will consistently result in a product with expected qualities.

7 Current Good Manufacturing Practices (CGMPs)

Validation:

establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting predetermined specifications and quality attributes.

8 Current Good Manufacturing Practices (CGMPs)

4. Assurance that production environment is suitable for its intended purpose.

5. Confirming that finished product has its purported characteristics with end-product testing, effective Quality Control methodology or combination of both.

6. Confirming that finished product retains its characteristics until its labeled expiration.

Current Good Manufacturing Practices (CGMPs)

7. Processes always conducted under control and as specified.

8. Prevention of product contamination, cross-contamination, and mix-up.

9. Adequate records and procedures for investigations and product failures.

10. Separation of functions / decisions of production and quality control.

Reasons for CGMP Inspections

- NDA/ANDA Pre-approval Inspections
- Changes in Plant Layout, or in Manufacturing Operations and Procedures
- Consumer Complaints
- Reports of Adverse Reactions
- Product Recalls

CGMPs Inspections
Objectives

- Determine Compliance with CGMPs
- Insure Drug Production and Control Procedures
- Result in Quality Products
- Identify Weaknesses and Deficiencies in Firms' Operations
- Obtain Correction of CGMP Deficiencies

CGMPs Inspections
Procedures

- Meet Most Responsible Official
- Present Government ID/ Written Notice of Inspection
- Obtain/verify Background Information, and Conduct Initial Plant Visit
- Conduct a Comprehensive or Focused CGMP Inspection
- Meet with Institutional Officials to Discuss Inspection Observations and Findings

ESSENTIAL
ALL DRUG MANUFACTURING
comply with
CGMP REGULATIONS
for FINISHED PHARMACEUTICALS

[21 CFR Parts 210 and 211]

14 Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) deems a drug to be adulterated if the methods used in, or the facilities or controls used for, its manufacturing, processing, packing, or holding do not conform to, or are not operated or administered in conformity with current good manufacturing practice to ensure that such drugs meet the requirements of the Act as to safety, has the identity and strength, and meets the quality and purity characteristics it purports or is represented to possess.

15 FDA's intends to relieve manufacturers of PET radiopharmaceutical drug products
from regulatory requirements when:

- unsafe handling of drug products may result
- inapplicable or inappropriate, or
- do not enhance safety or quality in the manufacture of drug products

16 REQUESTS for EXCEPTIONS and ALTERNATIVES
submitted as
CITIZEN PETITION
under
21 CFR 10.30

17 FDA will maintain a publicly available record of requests and Agency's action on such requests for
EXCEPTIONS and ALTERNATIVES

18 ALL REQUESTS for EXCEPTIONS or ALTERNATIVES should be clearly identified
"PET Request for EXCEPTION or ALTERNATIVE to the CGMP Regulations"

19 ALL CITIZEN PETITIONS should contain:

- Explanations,
- Descriptions, or
- Other information justifying an exception or alternative.

20 Options provide the opportunity to present
a variety of data and other information to support an
EXCEPTION or ALTERNATIVE

21 FDA may approve requests for an exception or alternative, when :

Compliance with the CGMP requirement is unnecessary;

Compliance with the requirement cannot be achieved;

Alternative procedures or controls satisfy the purpose of the requirement; or

Other justifications for an exception or alternative.

22

23

24 Manufacture of PET radiopharmaceutical drug products presents unique

concerns:

- Short physical half-life of positron emitting radionuclides
- Scale of manufacturing parallels demand of small number of patients
- Need to administer PET radiopharmaceutical drug products to patients

25 ☐ **Guidance for Industry**

- Does not attempt to address all sections of CGMP regulations
- Does not affect the specific requirements or standards for new drug applications
- Does not address specific issues related to INDs/NDAs

26 ☐ "Guidance for Industry Current Good Manufacturing Practices For Positron Emission Tomographic (PET) Drug Products"

supersedes

"Guide to Inspections of Liquid Injectable Radiopharmaceuticals Used in Positron Emission Tomography (PET)"

November 1993

27 ☐ **QUALITY CONTROL UNIT**

21 CFR 210.3(b)(15)

28 ☐ **PERSONNEL QUALIFICATIONS**

21 CFR 211.25

29 ☐ **BUILDINGS, FACILITIES, AND PERSONNEL RESPONSIBILITIES**

21 CFR 211.28 21 CFR 211.42
21 CFR 211.46 21 CFR 211.56

30 ☐ **FDA Guidance to Industry**

- Facility Design and Function
- Cleaning and Disinfection
- Equipment Testing
- Environmental Monitoring
- Building Cleanliness and Sanitation

31 ☐ **EQUIPMENT**

21 CFR 211.65 21 CFR 211.67
21 CFR 211.68

32 ☐ **FDA PET CGMP Guidance**

- Target Container and Tubing System
- Pyrogen (Endotoxin) Control
- Particle Accelerator
- Synthesis
- Computer Control of Equipment

33 ☐ **FDA Guidance:**

- Guide to Inspection of Computerized Systems in Drug Processing (February 1983)

- Guideline on General Principles of Process Validation" (May 1987)

34 ☐ **COMPONENTS, CONTAINERS, AND CLOSURES**

Subpart E

[21 CFR 211.80 to 21CFR 211.94]

35 ☐ **FDA PET CGMP Guidance**

- Coding, Identification, and Retesting of Components or Container-Closure Systems
- Finished Articles Used as Components or Container-Closure Systems
- Analytical and Identity Testing of Chemical Components
- Endotoxin Testing of Components

36 ☐ **PRODUCTION AND PROCESS CONTROLS**

21 CFR 211.110 21 CFR 211.113

37 ☐ **FDA PET CGMP Guidance**

- In-Process Sampling and Testing
- Sterilizing Filtration
- Aseptic Processing

38 ☐ **FDA Guidance:**

- Guide to Inspection of Computerized Systems in Drug Processing (February 1983)
- Guideline on General Principles of Process Validation (May 1987)

39 ☐ **PACKAGING & LABELING CONTROL**

21 CFR 211.122 to 21 CFR 211.134

40 ☐ **HOLDING AND DISTRIBUTION**

21 CFR 211.142

21 CFR 211.150

41 ☐ **TESTING AND RELEASE FOR DISTRIBUTION**

21 CFR 211.165

21 CFR 211.167

42 ☐ **FDA Guidance:**

- Guideline on Sterile Drug Products Produced by Aseptic Processing (June 1987)

43 ☐ **STABILITY TESTING & EXPIRATION DATING**

21 CFR 211.166

44 ☐ **FDA Guidance:**

- Draft Guideline for Submitting Supporting Chemistry Documentation in Radiopharmaceutical Drug Applications (November 1991)

45 ☐ **RESERVE SAMPLES**

21 CFR 211.170

46 ☐ **YIELDS**

21 CFR 211.110 21 CFR 211.113

47 ☐ **SECOND-PERSON CHECKS**

21 CFR 211. 25 21 CFR 211.134
21 CFR 211.101 21 CFR 211.103
21 CFR 211.122 21 CFR 211.182
21 CFR 211.186 21 CFR 211.188
21 CFR 211.194

48 ☐ **RECORDS AND REPORTS**

21 CFR 211.196 21 CFR 211.184

49 ☐ **REFERENCES**

Guide to Inspection of Computerized Systems in Drug Processing. February 1983

Guideline for Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices. December 1987

50 ☐ **REFERENCES**

Guideline on General Principles of Process Validation. May 1987

Guideline on Sterile Drug Products Produced by Aseptic Processing. June 1987

Draft Guideline for Submitting Supporting Chemistry Documentation in Radiopharmaceutical Drug Applications, FOD Doc No. 2009. November 1991

51 ☐ **Documentations available:**

DHHS/FDA/Center for Drug
Evaluation and Research
Division of Communications
Management (HFD-210)
5600 Fishers Lane
Rockville, Maryland 20857
FAX-ON-DEMAND (FOD):
1-800-342-2772 OR 1-301-827-0577

Microbiology Information for FDG ANDAs

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FDA. CDER. OGD.

1 ## Microbiology Information for FDG ANDAs

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FDA. CDER. OGD.

2 ## Microbiology Review

- A Separate Discipline from Chemistry
- Focus on Sterility and Endotoxins
- New Applications and Supplements

3 ## Descriptive Information - FDG Injection

- Product Description of the Final Dosage Form
  - Solution (approximate volume range)
  - Container and Closure
- Manufacturing Methods
- Sterilization Validations

4 ## Facility Description

- Manufacturing Site: Building Address
- Floor Plan
  - Process Flow, Room Numbers and Critical Environments
  - Critical Environment Specifications
  - Equipment

5 ## Manufacturing Process for Product

- Fluid Path Through Processing Equipment into Final Container
- Preparation of Bulk Solution (Carrier and Solvent) including Storage
- Product Solution Sterilization (Generally Filtration)
- Transfer of Solution into Product Container

6 ## Filtration Process Validation

- Specify the Filter
- Specify the Time, Pressure and Volume
- Specify the Integrity Test
- Validate the Membrane and Specifications

7 In-Process Sterilization

- Sterilization Process Parameters
  - Validation
  - Manufacturing
- Solution Components (certificates, filtration, etc.)
- Vials, Syringes, Stoppers
- Tubing, Mixing Vessels, Columns, Filters

8 Component Sterilization Validation

- Physical Measurement (heat and pressure)
- Biological Challenge (autoclaves and ovens)
- Endotoxin Challenge (ovens)

9 Fill Process Validation: Media Fills

- Simulated Manufacturing
- Methods: Media, Incubation, and Test Frequency
- Acceptance Criteria
- Data Summary (3 experiments)
- Actions Following Failures

10 Microbiological Monitoring

- Routine Monitoring of Personnel, Surfaces, Air, and Materials
  - Sampling Methods and Frequency
  - Cultivation: Media, Incubation Details
  - Special Tests; i.e., Yeast, Molds and Anaerobes
- Specifications or Limits
- Actions Following Exceeded Limits

11 Container and Closure Integrity

- Validate Final Product Dosage Form
- Assay
  - Challenge Methods
  - Detection Methods
  - Acceptance

12 Microbiology Release Tests

- Sterility

- Endotoxins
- Testing is required: 21 CFR 211.167(a)
- Product may be Released Before the Test is Finished: 21CFR 211.165(a)

13 ☐Sterility Tests

- Testing Laboratories
- Sample Type, Size, Time and Storage
  - Media, Incubation Parameters
  - Examination Procedures
  - Actions Following a Test Failure

14 ☐Endotoxins

- Testing Laboratories
- Methods: Include Materials, Controls and Validation
- Actions Following a Test Failure

15 ☐Formal Written Procedures

- List, Reference or Provide SOPs

16 ☐Maintenance of Product Quality: Stability

- (No special requirements)

17 ☐SUMMARY, Part 1

- Describe the dosage form
- Identify where it is made
- Describe the steps in its manufacture
- Specify and validate sterilization of components and equipment

18 ☐SUMMARY, Part 2

- Validate the aseptic process
- Describe the microbiological environmental monitoring
- Validate the container system integrity
- Specify and validate release tests