reasonable good-faith efforts to comply with the Act, and mitigating circumstances concerning its failure to operate an approvable automated system, were sufficient to permit ACF to use its inherent discretion to grant some relief short of state plan disapproval. South Carolina also argued that ACF must concede that it has discretion in so much as it grants conditional certification to states that are not fully compliant even though there is no explicit congressional authorization for such action. South Carolina further argued that regulations governing the administration of grants at 45 CFR Part 92 provide federal agencies with greater flexibility to address noncompliance than state plan disapproval, and that failure to consider the reasons for noncompliance would be fundamentally unfair and would amount to poor public policy by failing to consider South Carolina's actual performance in achieving the overall goals of the IV–D program.

ACF argued that the statutory language at section 454(24)(A) of the Act requires that a state operate an automated system which meets the specified requirements as a condition of plan approval, and affords ACF no discretion to excuse noncompliance. ACF argued that it has consistently stated in its program issuances that it is not authorized to provide federal IV–D funds to a state that does not have an approved IV–D state plan and that it is required to disapprove a state's plan where the state is not operating an automated system. ACF argued that court decisions that South Carolina cited in its brief are not applicable to the facts and the statutory requirements at issue here, and that 45 CFR Part 92 applies only where not inconsistent with the more specific statutory provisions addressing IV–D plan approval and the requirement of an operating automated system. ACF further argued that South Carolina presented no standards for granting relief from noncompliance short of plan disapproval, and that the presiding officer's authority is limited to recommending a decision as to whether or not a state plan meets federal requirements.

ACF's and South Carolina's briefs are available for inspection by the public, including persons and organizations who file timely requests to participate as parties or amici.

A ruling in ACF's favor on this threshold issue would limit the appeal to the sole question of whether or not South Carolina's state plan is in compliance with federal requirements. Given South Carolina's concession that it does not have an approvable automated data processing and information retrieval system for child support, such a ruling in ACF's favor would end the reconsideration process without an evidentiary hearing. Consequently, the presiding officer is affording interested parties the opportunity to participate prior to the issuance of a ruling.

A copy of this letter will appear as a Notice in the **Federal Register** and any person wishing to request recognition as a party will be entitled to file a petition pursuant to 45 CFR 213.15(b) with the Departmental Appeals Board within 15 days after that notice has been published. A copy of the petition should be served on each party of record at that time. The petition must explain how the issues to be considered have caused them injury and how their interest is within the zone of interests to be protected by the governing Federal statute. 45 CFR 213.15(b)(1). In addition, the petition must concisely state petitioner's interest in the proceeding, who will represent petitioner, and the issues on which petitioner wishes to participate. 45 CFR 213.15(b)(2). Additionally, if petitioner believes that there are disputed issues of fact which require an in-person evidentiary hearing, petitioner should concisely specify the disputed issues of fact in the petition, and also state whether petitioner intends to present witnesses. Petitioners may also, within 15 days after this notice has been published, request extensions of the time for requesting participation for the purpose of obtaining and reviewing copies of the parties' briefs.

Any party may, within 5 days of receipt of such petition, file comments thereon; the presiding officer will subsequently issue a ruling on whether and on what basis participation will be permitted.

Any interested person or organization wishing to participate as amicus curiae may also file a petition with the Board, which shall conform to the requirements at 45 CFR 213.15(c)(2). This petition, or a request for an extension of time to review the briefs, must be filed within 15 days after this notice, in time to permit the presiding officer an adequate opportunity to consider and rule upon it.

If the presiding officer denies ACF's request for a decision on the written record and rules that a hearing should be held, South Carolina shall be provided a notice of hearing, which shall be held not less than 30 days nor more than 60 days after the date that notice of the hearing is furnished to South Carolina. The notice of the hearing shall also be published in the **Federal Register** to afford notice to interested parties.

Any further inquiries, submissions, or correspondence regarding this matter should be filed in an original and two copies with Ms. Johnson at the Departmental Appeals Board, Room 637–D, Hubert H. Humphrey Building, 200 Independence Avenue, S.W., Washington, DC 20201, where the record in this matter will be kept.

That record is available for public inspection; interested persons or organizations seeking participation as parties or amici may contact Jeffrey Sacks, Board Staff Attorney, at 202–69–8011 (or at jsacks@os.dhhs.gov) to arrange for inspection and copying of the record. Each submission must include a statement that a copy of the submission has been sent to the other parties, identifying when and to whom the copy was sent. For convenience please refer to Board Docket No. A–99–80.

Dated: March 7, 2000.

Olivia A. Golden,

Assistant Secretary for Children and Families.

[FR Doc. 00–5921 Filed 3–9–00; 8:45 am]

BILLING CODE 4510–04–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00N–0553]

Positron Emission Tomography Drug Products; Safety and Effectiveness of Certain PET Drugs for Specific Indications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that the Commissioner of Food and Drugs (the Commissioner) has concluded that certain commonly used positron emission tomography (PET) drugs, when produced under conditions specified in approved applications, can be found to be safe and effective for certain indications specified in this document. FDA announces the approval procedures for these PET drugs and indications and invites manufacturers of these drugs to submit applications for approval under this document. The agency is taking this action in accordance with provisions of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). Elsewhere in this issue of the **Federal**

Register, FDA is issuing a draft guidance for industry entitled ''PET Drug Applications—Content and Format for NDA's and ANDA's,'' which is intended to assist manufacturers that submit applications for approval as specified in this document.

ADDRESSES: Submit applications for approval to the Center for Drug Evaluation and Research, Food and Drug Administration, 12229 Wilkins Ave., Central Document Room, Rockville, MD 20852. Copies of the published literature listed in the appendix to this document, FDA reviews of the literature, product labeling referenced in section IV of this document, and the transcript of the June 28 and 29, 1999, meeting of the Medical Imaging Drugs Advisory Committee (the Advisory Committee) will be on display at the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Electronic versions of these documents are available on the Internet at http://www.fda.gov/cder/regulatory/pet/default.htm.

FOR FURTHER INFORMATION CONTACT: John A. Friel, Center for Drug Evaluation and Research (HFD–200), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–1651, FAX 301–827–3056, e-mail: frielj@cder.fda.gov.

SUPPLEMENTARY INFORMATION:

I. Background

PET is a medical imaging modality that uses a unique type of radiopharmaceutical drug. PET drugs contain an atom that disintegrates principally by emission of a positron, which provides dual photons that are used for imaging, primarily for diagnostic purposes. Most PET drugs are produced using cyclotrons at locations (sometimes called ''PET centers'') that usually are in close proximity to the patients to whom the drugs are administered (e.g., in hospitals or academic institutions). Each PET drug ordinarily is produced under a physician's prescription and, due to the short half-lives of PET drugs, is injected intravenously into the patient within a few minutes or hours of production.

FDA has approved new drug applications (NDA's) for three PET drug products: Sodium fluoride F 18 injection, rubidium chloride 82 injection, and fludeoxyglucose (FDG) F 18 injection. In 1972, FDA approved NDA 17–042 for sodium fluoride F 18 injection as a bone imaging agent to define areas of altered osteogenic activity. The NDA holder ceased marketing this drug product in 1975. Rubidium chloride 82 injection (NDA 19–414), approved in 1989, is indicated for assessing regional myocardial perfusion in the diagnosis and localization of myocardial infarction. In 1994, FDA approved NDA 20–306, submitted by The Methodist Medical Center of Illinois (Methodist Medical), for FDG F 18 injection for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

On November 21, 1997, President Clinton signed into law the Modernization Act (Public Law 105–115). Section 121(c)(1)(A) of the Modernization Act directs FDA to establish appropriate procedures for the approval of PET drugs in accordance with section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355) and to establish current good manufacturing practice (CGMP) requirements for PET drugs. Prior to establishing these procedures and requirements, FDA must consult with patient advocacy groups, professional associations, manufacturers, and persons licensed to make or use PET drugs.

Under section 121(c)(2) of the Modernization Act, FDA cannot require the submission of NDA's or abbreviated new drug applications (ANDA's) for compounded PET drugs that are not adulterated under section 501(a)(2)(C) of the act (21 U.S.C. 351(a)(2)(C)) (i.e., that comply with United States Pharmacopeia (USP) PET compounding standards and monographs) for a period of 4 years after the date of enactment or 2 years after the date that the agency adopts special approval procedures and CGMP requirements for PET drugs, whichever is longer. However, the act does not prohibit the voluntary submission and FDA review of applications before these time periods expire.

In accordance with the Modernization Act, FDA has conducted several public meetings with a PET industry working group and other interested persons to discuss proposals for PET drug approval procedures and CGMP requirements. The industry working group, assembled by the Institute for Clinical PET (ICP), an industry trade association, includes representatives from academic centers, clinical sites, and manufacturers, and it was supported by the Society for Nuclear Medicine, the American College of Nuclear Physicians, and the Council on Radionuclides and Radiopharmaceuticals. After consulting with this working group and other interested persons, FDA decided to conduct its own reviews of the published literature on the safety and effectiveness of some of the most commonly used PET drugs for certain indications. The agency believed that this would be the most efficient way to develop new approval procedures for these drugs. Under current FDA policy, the agency may rely on published literature alone to support the approval of a new drug product under section 505 of the act (see FDA's guidance for industry entitled ''Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products'' (May 1998) and its draft guidance entitled ''Applications Covered by Section 505(b)(2)'' (December 1999)).

FDA reviewed the following PET drugs and indications for safety and effectiveness: (1) FDG F 18 injection for use in oncology and for assessment of myocardial hibernation, (2) ammonia N 13 injection for evaluation of myocardial blood flow, and (3) water O 15 injection for assessment of cerebral perfusion. FDA presented its preliminary findings on the safety and effectiveness of these drugs for certain indications to the ICP and others at public meetings. On June 28 and 29, 1999, FDA presented its findings on these drugs to the Advisory Committee. The Advisory Committee concluded that FDG F 18 injection and ammonia N 13 injection can be safe and effective for certain indications, although it recommended some revisions to the indications proposed by the agency. The Advisory Committee determined that, on the basis of the literature presented for its review, it was unable to conclude that water O 15 injection can be safe and effective for the proposed use of measuring cerebral blood flow in patients with cerebral vascular disorders associated with ischemia, hemodynamic abnormalities, occlusion, and other vascular abnormalities. FDA stated that it would conduct a more comprehensive review of the literature on the safety and effectiveness of water O 15 injection for this use and then ask the Advisory Committee to reconsider this drug at a subsequent meeting.

II. Highlights of This Document

As discussed in section III of this document, FDA concludes that FDG F 18 injection and ammonia N 13 injection, when produced under conditions specified in approved applications, can be found to be safe and effective for certain indications specified in that section and invites manufacturers of these drugs to submit applications for marketing approval [1].

[1] Section 121(c)(1) of the Modernization Act directs FDA to establish approval procedures and

This document states the approval procedures for these PET drugs for the particular indications identified. Depending on the circumstances discussed below, applications for approval of these drugs and indications may be either NDA's of the type described in section 505(b)(2) of the act or ANDA's submitted under section 505(j) of the act.

A 505(b)(2) application is an NDA for which at least one of the investigations that the applicant relies on to demonstrate the drug's safety and effectiveness was not conducted by or for the applicant, and the applicant has not obtained a right of reference or use from the person by or for whom the investigation was conducted.[2] A 505(b)(2) applicant can rely for approval on published literature or on FDA's findings of safety and/or effectiveness for an approved drug.

An ANDA is an application for approval of a ''generic'' version of an approved drug. An ANDA must include information to show that the drug has the same active ingredient(s), route of administration, dosage form, strength, and conditions of use recommended in the labeling of an approved drug. It must also contain information generally showing that the labeling of the generic drug is the same as that of the approved drug, that the generic drug is bioequivalent to the approved drug, and that the composition, manufacturing, and controls of the generic drug are sufficient to ensure its safety and effectiveness (section 505(j)(2)(A) of the act).

To aid manufacturers in submitting 505(b)(2) applications or ANDA's for FDG F 18 injection and ammonia N 13 injection for the indications reviewed by FDA, the agency is making available a draft guidance document, published elsewhere in this issue of the **Federal Register**, that provides specific instructions for each drug.

In addition, PET drug manufacturers may seek approval of applications for FDG F 18 injection for epilepsy and sodium fluoride F 18 injection for bone imaging by relying on the findings of safety and effectiveness made by the agency in approving the original NDA's for these drugs. Again, such applications may be either NDA's or ANDA's, depending on whether a manufacturer's proposed drug product is the same as an approved drug product.

If, after reviewing the relevant literature and consulting with the Advisory Committee, FDA concludes that water O 15 injection is safe and effective for a cerebral perfusion indication, the agency intends to issue a **Federal Register** notice announcing this conclusion and inviting manufacturers of this drug to submit applications for approval in accordance with the procedures discussed in this document.

In a future issue of the **Federal Register**, FDA intends to state its approach to applications for approval of other PET drugs and new indications for approved products in accordance with the Modernization Act.

III. PET Drugs for Which FDA Has Reviewed Published Literature

As discussed below, FDA generally agrees with and adopts the Advisory Committee's conclusions on the safety and effectiveness of FDG F 18 injection and ammonia N 13 injection, when produced under conditions specified in approved applications, for the indications stated in this document. In determining the safety and effectiveness of these drugs, FDA relied on the published literature and, where appropriate, previous agency determinations of safety or effectiveness. FDA obtained relevant articles in the published literature from the PET community and through the agency's own search of current, peer-reviewed literature. In evaluating a drug's effectiveness, FDA reviewed only those articles meeting the following criteria: (1) The studies involved prospective, controlled trials with an appropriate standard of truth (i.e., ''gold standard''); and (2) the article contained sufficient information to evaluate the study protocol, endpoints, statistical plan and methodology, sample size, accounting of enrolled patients, imaging protocol, blinding procedures, and image handling methodology.

FDA reviewed the literature to document the safety and effectiveness of these PET drugs on the basis of clinical pharmacology and biopharmaceutics, pharmacology and toxicology, and clinical and statistical information. The agency sought evidence that the reviewed drugs can provide useful clinical information related to their intended indications for use. The appendix to this document contains a list of published articles reviewed by FDA establishing that FDG F 18 injection and ammonia N 13 injection can be found to be safe and effective for specific indications when produced under conditions specified in approved applications. Copies of FDA's reviews of the published literature can be obtained in accordance with the **ADDRESSES** section of this document.

A. FDG F 18 Injection for Use in Myocardial Hibernation and Oncology

1. Safety

In evaluating the safety of FDG F 18 injection for both the oncology and myocardial hibernation indications, FDA considered the approximately two decades of clinical use of the drug and the conclusions the agency reached in approving NDA 20–306 for this drug. The currently labeled intravenous doses of FDG F 18 injection for epilepsy are 5 to 10 millicuries (mCi) in adults and 2.6 mCi in pediatrics. No significant adverse reactions have been reported for FDG F 18 injection. In addition, FDA found no reports of adverse reactions in the published literature on the effectiveness of FDG F 18 injection or in a recent article by Silberstein and others (1996) reporting the results of a 5-year prospective study on drugs used in nuclear medicine at 18 collaborating institutions.

The literature and FDA's finding on the safety of FDG F 18 injection in NDA 20–306 indicate that for an intravenous dose of 10 mCi of the drug, the critical target organ (the bladder) absorbs only 6.29 rems based on a fixed bladder content over a 3-hour period. For higher doses, the level and extent of radiation absorbed by the bladder walls can be manipulated with hydration and shorter voiding intervals to decrease radiation exposure. On the basis of this information, a 10-mCi dose of FDG F 18 injection appears to pose a relatively low risk to adult patients.

2. Safety and Effectiveness for Identifying Hibernating Myocardium

FDA's search of the recent published literature on FDG F 18 injection yielded 632 articles, from which the agency identified 10 articles that: (1) Met the review criteria; (2) evaluated patients with coronary artery disease (CAD) and left ventricular dysfunction; and (3) considered whether FDG F 18 image findings before coronary revascularization could predict the functional outcome of regions of the left ventricle after revascularization. All of these articles involved adequate and well-controlled clinical trials. FDA also reviewed several other articles in support of the potential clinical usefulness of FDG F 18 for such cardiac evaluations.

CGMP's for all PET drugs, without any exclusion for compounded PET drugs. Consequently, references in this document to PET drugs that are ''produced'' or ''manufactured'' include compounded PET drugs.

[2] A right of reference is the authority to rely upon an investigation for approval of an application and includes the ability to make the underlying raw data available for FDA audit, if necessary (21 CFR 314.3(b)).

The use of FDG F 18 injection for this purpose is based on the premise that reversibly injured myocytes can metabolize glucose but irreversibly injured myocytes cannot. Based on its review of the literature, FDA concludes that a 10-mCi dose (for adults) of FDG F 18 injection produced under conditions specified in an approved application can be found to be safe and effective in PET imaging of patients with CAD and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function.

3. Safety and Effectiveness for Evaluating Glucose Metabolism in Oncology

Published articles on the use of FDG F 18 for oncology imaging first appeared in the 1980's. The use of FDG F 18 injection in oncology is based on different rates of glucose metabolism that are expected to occur in benign and malignant tissues.

FDA's search of the published literature revealed about 150 articles involving clinical trials with FDG F 18 injection in oncology. Of these, the agency identified 16 articles that met the review criteria and had both a study population of greater than 50 and histopathologic confirmation of the type of malignancy. Two of the articles involved adequate and well-controlled trials. On the basis of these and other supportive studies, FDA concludes that a 10-mCi dose (for adults) of FDG F 18 injection produced under conditions specified in an approved application can be found to be safe and effective in PET imaging for assessing abnormal glucose metabolism to assist in evaluating malignancy in patients with known or suspected abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer.

B. Ammonia N 13 Injection for Assessing Myocardial Perfusion

The published literature contains reports of clinical investigations involving ammonia N 13 dating back to the 1970's. A principal focus of these studies has been the use of ammonia N 13 injection to evaluate myocardial blood flow.

1. Safety

Ammonia is a ubiquitous substance in the body, and its metabolism and excretion are well understood. The maximum amount of ammonia in a typical dose of ammonia N 13 injection is extremely small compared to the amount of ammonia produced by the body. The reviewed published literature does not identify any adverse events following the administration of ammonia N 13 injection.

The literature indicates that after a total intravenous dose of approximately 25 mCi of ammonia N 13 injection, the critical target organ (bladder wall) absorbs only 1.28 rems. Therefore, a 10-mCi dose of ammonia N 13 injection appears to pose a relatively low risk to adult patients.

2. Safety and Effectiveness for Assessing Myocardial Perfusion

FDA's search of the published literature revealed 76 articles on the use of ammonia N 13 injection for assessing myocardial perfusion. Of these, 17 articles met the review criteria and provided a comparison of myocardial perfusion results of ammonia N 13 injection to a recognized standard of myocardial perfusion or to other appropriate comparators. Two articles discussed the results of adequate and well-controlled studies evaluating the effectiveness of ammonia N 13 injection in assessing myocardial perfusion. On the basis of these studies, FDA concludes that a 10-mCi dose (for adults) of ammonia N 13 injection produced under conditions specified in an approved application can be found to be safe and effective in PET imaging of the myocardium under rest or pharmacological stress conditions to evaluate myocardial perfusion in patients with suspected or existing CAD.

IV. Applications for Approval of Reviewed PET Drugs and Sodium Fluoride F 18 Injection

A. Types of Applications Required for Reviewed PET Drugs

Based on its review of the published literature and the recommendations of the Advisory Committee, FDA has determined that FDG F 18 injection and ammonia N 13 injection, when produced under conditions specified in an approved application, can be found to be safe and effective for the specified indications. Approved applications are required because these drugs cannot be deemed generally recognized as safe and effective under section 201(p)(1) and (p)(2) of the act (21 U.S.C. 321(p)(1) and (p)(2)), making them new drugs subject to regulation under section 505 of the act. Congress recognized that PET drugs are new drugs when it directed FDA, in section 121(c)(1)(A)(i) of the Modernization Act, to establish appropriate approval procedures for these drugs ''pursuant to section 505'' of the act.

A principal reason why PET drugs are new drugs and not generally recognized as safe and effective is that the approximately 70 PET centers differ considerably in the way they formulate and manufacture these drugs. Such variations in drug constituents and in manufacturing procedures can significantly affect the identity, strength, quality, and purity of the drugs in a manner that may well adversely affect their safety and effectiveness. For example, these PET drugs are injectable products that cannot be safe unless they are at least sterile and pyrogen-free. Therefore, FDA must verify that appropriate conditions and procedures regarding sterility and pyrogenicity exist at each manufacturing site.

Stability concerns are another example of why formulation and manufacturing techniques must be considered in evaluating safety and effectiveness. Without adequate controls, PET drugs may be unstable when produced in high radioconcentrations (as occur at some PET centers) due to radiolytic degradation of the drug substance. Such degradation can result in a subpotent drug as well as administration of radioactive moieties other than the intended drug substance. Depending on their specific localization, such moieties can cause excessive radiation of nontargeted tissues or interfere with imaging. This can make a drug product unsafe in a susceptible population or result in misdiagnosis.

Another aspect of PET drug production that can adversely affect safety is the potential for the development of impurities in the finished product. Some of these impurities would pose a threat to the health of patients.

For these and other reasons, the agency cannot conclude that these PET drugs are generally recognized as safe and effective for the above-noted indications and therefore needs to review information on how each drug product is formulated and produced at each manufacturing site. Because these PET drugs are not generally recognized as safe and effective, they are new drugs for which approved NDA's or ANDA's are required for marketing under section 505(a) of the act and part 314 (21 CFR part 314).

As previously noted, if a PET drug fully complies with all USP standards and monographs pertaining to PET drugs, an application for approval of such drug is not required until 2 years after FDA establishes approval procedures and CGMP requirements for

PET drugs. Although submission of applications is not required at this time, FDA encourages the manufacturers of FDG F 18 injection and ammonia N 13 injection to submit applications for approval under section 505(b)(2) or (j) of the act, as discussed below in sections IV.A.1 and IV.A.2, as soon as possible.

1. Applications for FDG F 18 Injection

As noted above, there is already an approved application (NDA 20–306, held by Methodist Medical) for FDG F 18 injection for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures. To obtain approval to market their FDG F 18 injection products for the new (myocardial and oncological) indications discussed in section III.A of this document, initially all applicants except Methodist Medical should submit 505(b)(2) applications. FDA anticipates that such applicants will seek approval for all three indications for FDG F 18 injection. In that case, applicants should reference the safety and effectiveness data in the published literature listed in the appendix to this document for the myocardial and oncological indications for FDG F 18 injection and the findings of safety and effectiveness regarding NDA 20–306 for the epilepsy-related indication in accordance with § 314.54. Methodist Medical may, if it chooses, submit a supplemental NDA for each of the two new indications in accordance with section 506A of the act (21 U.S.C. 356a) and this document. The supplemental applications need only reference the information in the appendix to this document. Applicants need not conduct their own clinical trials or submit copies of the articles listed in the appendix.

The drug product that is the subject of the first approved NDA for FDG F 18 injection for the indications stated in section III.A of this document (myocardial hibernation and oncology) most likely will be the reference listed drug for these indications under section 505(j)(2)(A) of the act and § 314.3. FDA will continue to review as 505(b)(2) applications those applications for FDG F 18 injection that have already been filed at the time of approval of the first application. After FDA approves the first application for FDG F 18 injection submitted in response to this document, subsequent applications for approval of the same drug for the same indications should generally be submitted as ANDA's under section 505(j) of the act and § 314.92(a)(1), rather than as 505(b)(2) applications.[3] FDA anticipates that in many cases, NDA 20–306 will be the appropriate reference listed drug for such ANDA's.[4] However, as 505(b)(2) applications are approved, the agency may identify additional products as reference listed drugs.

If a PET drug manufacturer's FDG F 18 injection product has an active ingredient, route of administration, dosage form, or strength that differs from that of a listed drug, the applicant would probably submit a 505(b)(2) application. Alternatively, the applicant could submit an ANDA after obtaining approval of a ''suitability petition'' for such a drug, although this would likely be a less efficient means of obtaining marketing approval.[5] (Because FDA has already approved a suitability petition granting permission to submit an ANDA for FDG F 18 injection with a different strength (i.e., 1.6 to 58.4 mCi/mL at the end of bombardment) than that of the reference listed drug, an ANDA applicant could, if it desired, make reference in its own application to the strength in the approved suitability petition.)

2. Applications for Ammonia N 13 Injection

Because there is no approved ammonia N 13 injection product for any indication, initially all manufacturers of this drug should submit 505(b)(2) applications. Applicants should reference the published literature on the safety and effectiveness of ammonia N 13 injection for assessment of myocardial perfusion listed in the appendix to this document.

After FDA approves the first application for ammonia N 13 injection for assessing myocardial perfusion, subsequent applications for approval of the same drug for the same indication could be submitted as ANDA's. However, a 505(b)(2) application (or a suitability petition) should be submitted if the active ingredient, route of administration, dosage form, or strength of the applicant's ammonia N 13 injection product differs from that of a listed drug.

B. Types of Applications Required for Sodium Fluoride F 18 for Bone Imaging

FDA approved sodium fluoride F 18 injection (NDA 17–042) in 1972 as a bone imaging agent to define areas of altered osteogenic activity. The current NDA holder, Nycomed Amersham, stopped marketing the drug in March 1975.

As an approved drug, sodium fluoride F 18 injection would normally be listed in the ''Approved Drug Products with Therapeutic Equivalence Evaluations'' (generally known as the ''Orange Book''), in accordance with section 505(j)(7) of the act. However, certain drug products, including sodium fluoride F 18 injection, that were approved for safety and effectiveness but were no longer marketed on September 24, 1984, are not included in the Orange Book. In implementing section 505(j)(7) of the act, FDA decided not to retrospectively review products withdrawn from the market prior to that date. Rather, the agency determines on a case-by-case basis whether such drugs were withdrawn from the market for safety or effectiveness reasons. FDA must make a determination as to whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before it may approve an ANDA that refers to the listed drug (§ 314.161(a)(1)).

FDA reviewed its records and, under § 314.161, determined that sodium fluoride F 18 injection was not withdrawn from sale for reasons of safety or effectiveness. Accordingly, the agency will list sodium fluoride F 18 injection in the Orange Book's ''Discontinued Drug Product List'' section, which delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. Because sodium fluoride F 18 injection was not withdrawn from sale for reasons of safety or effectiveness, it is still a listed drug, and FDA can approve ANDA's that refer to it. FDA therefore invites those PET centers whose sodium fluoride F 18 injection product is the

[3] Under § 314.101(d)(9), FDA may refuse to file a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act.

[4] For the existing reference listed drug for FDG F 18 injection (NDA 20–306), the active ingredient is FDG F 18, the route of administration is intravenous, the dosage form is injection, and the strength is 4.0 to 40 mCi/milliliters (mL) at the end of synthesis.

[5] Under section 505(j)(2)(C) of the act, FDA will approve a petition seeking permission to file an ANDA for a drug that has an active ingredient, route of administration, dosage form, or strength that differs from that of a listed drug unless the agency finds that: (1) Investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage from, or strength that differ from the listed drug; or (2) a drug with a different active ingredient may not be evaluated for approval as safe and effective on the basis of the information required to be submitted in an ANDA. If FDA approves a suitability petition for a drug product, the applicant may then submit an ANDA. However, if FDA concludes that additional studies are necessary to show the safety and/or effectiveness of the drug proposed in the petition, the applicant would need to submit a 505(b)(2) application to obtain marketing approval.

same as the reference listed drug to submit ANDA's.[6]

If a sponsor's sodium fluoride F 18 injection product is not the same as the listed drug, the sponsor should submit a 505(b)(2) application (or a suitability petition) rather than an ANDA. FDA anticipates that this will be the case with most manufacturers of sodium fluoride F 18 injection because the strength of their product is likely to differ from that of the listed drug.

C. Additional Guidance on Submission of Applications and Labeling

FDA is issuing a draft guidance document, published elsewhere in this issue of the **Federal Register**, to assist PET drug manufacturers in submitting NDA's and ANDA's for FDG F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection in accordance with this document. Among other things, the draft guidance addresses the chemistry, manufacturing, and controls information that should be provided in applications for these drugs.

FDA has developed suggested labeling for FDG F 18 injection and ammonia N 13 injection products for the indications discussed above. The suggested labeling for FDG F 18 injection also includes the previously approved indication of identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures. A manufacturer seeking approval of FDG F 18 injection, ammonia N 13 injection, or sodium fluoride F 18 injection in accordance with this document should submit product labeling that is consistent with the recommended labeling. This labeling is available on the Internet at http://www.fda.gov/cder/regulatory/pet and is on display in FDA's Dockets Management Branch (address above). The labeling also will be included in the forthcoming draft guidance document on the submission of applications in accordance with this document.

D. Pediatric Assessments

Under § 314.55(a), each application for a new active ingredient or new indication must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support specific dosing and administration for the drug. When the course of a disease and the effects of a drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients. In addition, FDA may defer submission of some or all pediatric assessments until after approval of a drug product for use in adults, including when the agency determines that pediatric studies should be delayed until additional safety or effectiveness data have been collected (§ 314.55(b)).

The original application for FDG F 18 injection (NDA 20–306) is approved for epilepsy in pediatric patients. Based on available radiation dosimetry data for different ages and information on the use of glucose during pediatric development, FDA concludes that sufficient data are available to support the statements on the pediatric use of FDG F 18 injection found in the labeling referenced in section IV.C of this document.

Regarding ammonia N 13 injection, information exists on the known effects of ammonia on the human body, the normal blood levels of ammonia for different ages, the amount of ammonia N 13 injection typically administered to patients, and the radiation dosimetry of the drug for different ages. Therefore, FDA concludes that sufficient data are available to support the statements on the pediatric use of ammonia N 13 injection found in the labeling referenced in section IV.C of this document.

Limited data are available that are relevant to the pediatric use of sodium fluoride F 18 injection for use in defining areas of altered osteogenic activity. Therefore, FDA is deferring the pediatric assessments required under § 314.55(a) for sodium fluoride F 18 injection for this indication until 5 years after the date that the agency adopts approval procedures and CGMP requirements for PET drugs. This deferral will allow the agency to obtain additional safety and effectiveness information on the use of sodium fluoride F 18 injection before determining what pediatric studies may be necessary.

E. User Fees

Under section 736(a)(1)(A)(ii) of the act (21 U.S.C. 379h(a)(1)(A)(ii)), FDA assesses an application fee for any human drug application as defined in the statute. No application fee is required for an ANDA or for a supplement for which clinical data are not required.

An application fee normally would be assessed for a 505(b)(2) application for FDG F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection submitted in accordance with this document. However, FDA intends to grant a waiver of application fees for these drugs. Under section 736(d)(1) of the act, FDA can grant a waiver or reduction in fees for several reasons, including when assessment of a fee would present a significant barrier to innovation because of limited resources available to the applicant or other circumstances (section 736(d)(1)(B) of the act).

FDA finds that, because of the unique circumstances surrounding the regulation of PET drugs, assessment of an application fee on the PET drugs noted above would present a significant barrier to innovation. FDA is aware that Congress directed the agency to develop appropriate approval procedures and CGMP requirements for PET drugs to ''take account of the special characteristics of positron emission tomography drugs and the special techniques and processes required to produce these drugs'' (section 121(c)(1)(A) of the Modernization Act). One of Congress' goals in enacting section 121 of the Modernization Act is to promote the availability of FDA-approved PET drug products for the patients who need them. As noted in the Senate report on the Modernization Act, most of the approximately 70 PET centers in the United States are part of academic medical centers (S. Rept. No. 43, 105th Cong., 1st Sess., at 53 (1997)). The report states that these academic medical centers are facing unprecedented cost pressures, suggesting that many PET centers would likely close without some kind of regulatory relief. The report emphasizes that if PET centers close, the benefits of PET would be unavailable to patients who need this diagnostic technology.

FDA finds that Congress intended for the agency to ease the regulatory burden on PET centers, including by providing waivers of user fees in appropriate circumstances. FDA further concludes that a waiver of the application fees for applications seeking approval of FDG F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection products submitted in response to this document is consistent with the congressional goal of promoting the availability of FDA-approved PET drugs. Without a fee waiver, there may be a disincentive for manufacturers of these PET drugs to submit NDA's under section 505(b)(2) of the act because an application fee normally would be assessed on each application submitted only until FDA approves the first NDA for a particular drug and indication. Once FDA approves such a product, subsequently submitted 505(b)(2)

[6] For the reference listed drug, the active ingredient is sodium fluoride F 18, the route of administration is intravenous, the dosage form is injection, and the strength is 2.0 mCi/mL at the time of calibration.

applications for the particular drug and indication will not be assessed an application fee.

On the other hand, if an applicant hoped to obtain market exclusivity (as discussed in section IV.F of this document), it would have an incentive to be the first to submit and obtain approval of an NDA for one of these PET drugs. Therefore, for the reasons noted above, FDA will waive the application fee for NDA's for FDG F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection products submitted in accordance with this document, but only if the applicant submits with its NDA a statement that it waives any right to market exclusivity to which it may be entitled under the act.

F. Patent Protection and Market Exclusivity

PET drug products approved by FDA may be protected from competition by patents issued by the U.S. Patent and Trademark Office or by periods of market exclusivity granted by FDA at the time of approval. Patent and exclusivity protections may affect the approval of competing 505(b)(2) applications and ANDA's.

Applicants submitting NDA's under section 505(b) of the act, including 505(b)(2) applications, must file with the application, in accordance with § 314.53, a list of the patent numbers and expiration dates for each patent that claims the drug substance, drug product (formulation and composition), or method of using the drug that is the subject of the application. No other patents may be submitted, including process patents covering the manufacture of the drug. Additional patent information must be submitted within 30 days of approval of an application or, in the case of newly issued patents, within 30 days of issuance of the patent. If an application is approved, FDA will publish the patent information in the Orange Book.

Certain PET drugs may also be eligible for patent term extensions under 35 U.S.C. 156. Patent term extensions are issued by the U.S. Patent and Trademark Office.

Sponsors submitting NDA's for PET drug products may be eligible for market exclusivity under the act. There are four types of exclusivity available: (1) 5-year new chemical entity exclusivity, (2) 3-year exclusivity for applications that require new clinical trials, (3) 6-month pediatric exclusivity, and (4) 7-year exclusivity for drugs intended to treat rare diseases or conditions (i.e., ''orphan drugs''). Eligibility for exclusivity depends on, among other things, the characteristics of the drug product and the type of studies conducted by the applicant. A sponsor who believes its drug product is entitled to exclusivity must submit supporting information in its NDA (§ 314.50(j)). Applicants interested in determining whether a PET drug product may be eligible for exclusivity are encouraged to discuss the issue with the Center for Drug Evaluation and Research's Division of Medical Imaging and Radiopharmaceutical Drug Products.

A drug product that contains a new chemical entity may be eligible for 5 years of market exclusivity under sections 505(c)(3)(D)(ii) and (j)(5)(D)(ii) of the act and the regulations at § 314.108. Whether a drug qualifies for new chemical entity exclusivity depends on whether the active moiety has been approved in another application submitted under section 505(b) of the act. The ''active moiety'' is, in general terms, ''the molecule or ion * * * responsible for the physiological or pharmacological action of the drug substance'' (§ 314.108(a)). A drug product containing a new chemical entity may be eligible for 5 years of exclusivity even if the drug product is submitted in a 505(b)(2) application that relies for approval on literature reviewed by FDA supporting the safety and effectiveness of the drug. For new chemical entity exclusivity, there is no requirement that the sponsor conduct clinical trials to obtain the approval.

New chemical entity exclusivity generally bars submission of any 505(b)(2) application or ANDA for a drug containing the same active moiety for 5 years from the date the new chemical entity is approved.[7] If at the time the first NDA for an active moiety is approved and given exclusivity, other applicants have already submitted 505(b)(2) applications for products with the same active moiety, the agency may review and approve those applications, notwithstanding the exclusivity the first drug product obtained at the time of approval (54 FR 28872 at 28901, July 10, 1989). The first drug product's exclusivity will only bar submission of new 505(b)(2) applications or ANDA's. Therefore, if applications are submitted relatively close in time, new chemical entity exclusivity may not block approval of multiple 505(b)(2) applications for PET drugs with the same active moiety.

Certain PET drug products may also be eligible for 3 years of market exclusivity under section 505(c)(3)(D)(iii) and (c)(3)(D)(iv) and (j)(5)(D)(iii) and (j)(5)(D)(iv) of the act and § 314.108(b)(4). Three-year exclusivity is granted when an NDA contains reports from new clinical studies conducted or sponsored by the applicant and those studies are essential to approval of the application. Bioequivalence and bioavailability studies are not clinical studies that qualify for exclusivity. A 505(b)(2) application may be eligible for 3-year exclusivity if it relies in part on published literature or on FDA's findings on the safety or effectiveness of a PET drug, but also contains reports of new clinical studies conducted by the sponsor that are essential to the approval of, for example, a new use for the drug.

If a drug product is given 3 years of exclusivity, FDA is barred from approving any 505(b)(2) application or ANDA for the same drug product, or change to the product, as that for which the exclusivity was granted. For example, if an applicant obtains 3 years of exclusivity for a new indication for a PET drug, FDA may not approve an ANDA for that indication for 3 years. However, the agency may approve an ANDA for any previously approved indications not protected by the exclusivity.

Sponsors of PET drug products may also obtain pediatric exclusivity in accordance with section 505A of the act (21 U.S.C. 355a). To be eligible to obtain 6 months of pediatric exclusivity, a drug product must have patent or exclusivity protection to which the pediatric exclusivity period can attach. A drug product that has no patents listed in the Orange Book or other market exclusivity will not be eligible for pediatric exclusivity. To obtain pediatric exclusivity, a sponsor must conduct studies as described in a written request issued by FDA and must submit those studies within the timeframe described in the written request and in accordance with the filing requirements. Detailed information on qualifying for pediatric exclusivity is available in FDA's guidance for industry entitled ''Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act'' (64 FR 54903, October 8, 1999).

A PET drug product intended for the diagnosis of a rare disease or condition (one that affects fewer than 200,000 people in the United States) may be eligible for 7 years of orphan drug exclusivity under sections 526 and 527 of the act (21 U.S.C. 360bb-360cc). Obtaining orphan drug exclusivity is a two-step process. An applicant must

[7] An exception to this 5-year bar permits an applicant to submit a 505(b)(2) application or ANDA after 4 years if it contains a certification of invalidity or noninfringement for a patent listed for the approved drug.

seek orphan drug designation for its drug prior to submitting an NDA. If FDA designates the drug as an orphan drug and then approves it for the designated indication, the drug will receive orphan drug exclusivity. Orphan drug exclusivity bars FDA from approving another application from a different sponsor for the same drug for the same indication for a 7-year period.

A sponsor who is entitled to any type of exclusivity for a PET drug product may waive such exclusivity to allow one or more applicants to submit applications for the product. For example, if the sponsor of a 505(b)(2) application for a PET drug were to obtain 5-year exclusivity, a complete waiver of such exclusivity would enable other applicants to immediately submit 505(b)(2) applications and ANDA's for a drug containing the same active moiety.

Information regarding patents and exclusivity periods for approved drug products is published in the Orange Book. This information is important for applicants considering submitting ANDA's or 505(b)(2) applications for PET drugs. If a reference listed drug for an ANDA or a listed drug for a 505(b)(2) application has listed patents, the ANDA or 505(b)(2) application will be required to contain certifications regarding those patents (see § 314.94(a)(12) for ANDA's, § 314.50(i) for 505(b)(2) applications).

G. CGMP

As noted in section I of this document, the Modernization Act directs FDA to develop appropriate CGMP requirements for PET drugs. At a public meeting held on February 19, 1999, FDA discussed its preliminary approach to CGMP's for PET drugs with the PET industry working group and other attendees. In response to comments from the PET community, FDA revised its CGMP preliminary draft regulations. These preliminary draft provisions were discussed at a public meeting held on September 28, 1999. FDA intends to propose regulations on CGMP's for PET drugs in a forthcoming issue of the **Federal Register**, after obtaining additional public input.

H. Preapproval Inspections

FDA is authorized under the act to inspect the facilities to be used in the manufacture of a drug product prior to granting approval of an application to ensure that the facilities and controls used to manufacture the drug are adequate to preserve its identity, strength, quality, and purity (sections 505(d)(3) and (k)(2) and 704(a)(1) of the act (21 U.S.C. 374(a)(1)); see also § 314.125(b)(12)). FDA will not inspect PET drug manufacturing facilities for compliance with CGMP's until 2 years after the date that the agency establishes CGMP requirements for such drugs. However, until such time, if an application for approval of a PET drug is submitted, FDA will conduct an inspection to determine whether the facilities and controls used to manufacture the proposed drug product conform to the USP's PET compounding standards and monographs, in accordance with section 501(a)(2)(C) of the act (21 U.S.C. 351(a)(2)(C)),[8] and to verify other aspects of an NDA or ANDA submission.

V. Approval Procedures for Other PET Drugs and Indications

FDA has not yet addressed the procedures for approval of other PET drugs and of new indications for approved PET drugs. In FDA's proposed rule on the evaluation and approval of in vivo radiopharmaceuticals used for diagnosis and monitoring, published in the **Federal Register** of May 22, 1998 (63 FR 28301 at 28303), the agency stated that it expected the standards for determining safety and effectiveness set forth in the proposed rule to apply to PET drugs, which are one type of radiopharmaceutical.

FDA published its final rule on diagnostic radiopharmaceuticals in the **Federal Register** of May 17, 1999 (64 FR 26657). The final rule adds part 315 (21 CFR part 315), which addresses how FDA will interpret and apply certain provisions in part 314 to evaluate the safety and effectiveness of diagnostic radiopharmaceuticals. The agency also issued a draft guidance for industry entitled ''Developing Medical Imaging Drugs and Biologics,'' which, when finalized, will provide information on how the agency will interpret and apply the provisions of the final rule. In a future issue of the **Federal Register**, FDA intends to address whether and, if so, how new part 315 and the medical imaging guidance should be modified in their application to PET drugs.

VI. Conclusions

The Commissioner has concluded that FDG F 18 injection, when produced under the conditions specified in an approved application, can be found to be safe and effective in PET imaging in patients with CAD and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function, as discussed in section III.A.1 and III.A.2 of this document. The Commissioner also has concluded that FDG F 18 injection, when produced under the conditions specified in an approved application, can be found to be safe and effective in PET imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer, as discussed in section III.A.1 and III.A.3 of this document. In addition, the Commissioner has concluded that ammonia N 13 injection, when produced under the conditions specified in an approved application, can be found to be safe and effective in PET imaging of the myocardium under rest or pharmacological stress conditions to evaluate myocardial perfusion in patients with suspected or existing CAD, as discussed in section III.B of this document. The Commissioner bases these conclusions on FDA's review of the published literature on these uses and on the recommendation by the agency's Medical Imaging Drugs Advisory Committee that FDA find these drugs to be safe and effective for these indications.

In addition, manufacturers of FDG F 18 injection and sodium fluoride F 18 injection may rely on prior agency determinations of the safety and effectiveness of these drugs for certain epilepsy-related and bone imaging indications, respectively, in submitting either 505(b)(2) applications or ANDA's for these drugs and indications.

Applications for approval of these PET drug products should be submitted in accordance with sections III and IV of this document as well as the guidance documents and product labeling referenced in section IV of this document.

VII. Assistance for Applicants

If you have questions about this document or need help in preparing an application for approval of one of the PET drugs discussed above, contact John A. Friel (address above); also, application forms are available from Friel's office. For further information and assistance visit the Internet on PET drugs at http//www.fda.gov/cder/regulatory/pet/default.htm.

[8] Section 501(a)(2)(C) of the act, established by the Modernization Act, requires that PET drugs be produced in conformity with the USP's PET drug compounding standards and monographs. This provision will expire 2 years after the date on which FDA establishes approval procedures and CGMP requirements for PET drugs.

VIII. Availability of Published Literature and Other Resources

The published literature referenced in section III of this document is listed in the appendix to this document. Copies of the published literature, FDA reviews of the literature, product labeling referenced in section IV of this document, and the transcript of the June 28 and 29, 1999, Advisory Committee meeting will be on display in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

Appendix: Published Literature on the Safety and Effectiveness of Reviewed PET Drugs

I. Published Literature on FDG F 18 Injection:

A. Pharmacology, Toxicology, and Biopharmaceutics

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Dated: March 6, 2000.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Food and Drug Administration/Industry Exchange Workshop on Medical Device Quality Systems Inspection Technique (QSIT); Public Workshops; Addendum

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

The Food and Drug Administration (FDA) is announcing an additional workshop in the series of FDA/Industry Exchange Workshops that were conducted in 1999. The original list of workshops was published in the **Federal Register** of September 10, 1999. Topics for discussion include: Development of Quality Systems Inspection Technique (QSIT), Compliance Program and Warning Letter (Pilot), Management Controls, Corrective and Preventive Action, Design Controls, and Industry Perspective QSIT. This additional workshop will enhance the medical device community's understanding of QSIT, and the device industry's establishment of effective quality systems, thereby preventing regulatory problems during inspections.

Date and Time: The meeting will be held on Wednesday, March 29, 2000, 8:30 a.m. to 4:30 p.m.

Location: The meeting will be held at Carlsbad: Four Seasons Resort—Aviara, 7100 Four Seasons Point, Carlsbad, CA 92009, 760–603–6800.

Registration: Send registration information (including name, title, firm name, address, telephone, and fax number) along with $140 to the registrar by Monday, March 20, 2000. Fees cover refreshments, organization and site cost, and materials. Space is limited, therefore interested parties are encouraged to register early. Please arrive early to ensure prompt registration. If you need special accommodations due to a disability, please inform the registrar at least 7 days in advance of the workshop. A sample registration form is provided at http://www.fda.gov/cdrh/meetings/qsitmeetca.html.

Contact: Marcia Madrigal, FDA, Pacific Region (HFR PA–150), 1301 Clay St., suite 1180–N, Oakland, CA 94612–5217, 510–637–3980.

Registrar and cosponsor: Joyce W. Williams, San Diego Regulatory Affairs Network (SDRAN), c/o Arena Pharmaceuticals, Inc., 6166 Nancy Ridge Dr., San Diego, CA 92121, 858–453–7200, ext. 227, FAX 858–453–7210, e-mail: jwilliams@arenapharm.com.

SUPPLEMENTARY INFORMATION: In the fall of 1999, FDA field offices began using the QSIT nationwide as the tool for medical device inspections. QSIT was developed using a collaborative effort with stakeholders and tested in the three districts. The original list of workshops was published in the **Federal Register** of September 10, 1999 (64 FR 49192).

This additional workshop further implements the FDA Plan for Statutory Compliance (developed under section 406 of the FDA Modernization Act (21 U.S.C. 393)) through working more closely with stakeholders and ensuring access to needed scientific and technical expertise. It also implements a Small Business Regulatory Enforcement Fairness Act (Public Law 104–121) goal of providing outreach activities by Government agencies directed to small businesses.

Dated: March 6, 2000.

William K. Hubbard,

Senior Associate Commissioner for Policy, Planning, and Legislation.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00D–0892]

Draft Guidance for Industry on the Content and Format of New Drug Applications and Abbreviated New Drug Applications for Certain Positron Emission Tomography Drug Products; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled ''PET Drug Applications —Content and Format for NDA's and ANDA's.'' The draft guidance is intended to assist manufacturers of certain positron emission tomography (PET) drugs in submitting new drug applications (NDA's) or abbreviated new drug applications (ANDA's) in accordance with a notice entitled ''Positron Emission Tomography Drug Products; Safety and Effectiveness of Certain PET Drugs for Specific Indications'' published elsewhere in this issue of the **Federal Register**.

DATES: Submit written comments on the draft guidance and the collection of information provisions by June 8, 2000. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Copies of this draft guidance for industry are available on the Internet at http:/www.fda.gov/cder/guidance/index.htm and at http:/www.fda.gov/cder/regulatory/pet. Submit written requests for single copies of the draft guidance 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 the office in processing your requests. Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Requests and comments should be identified with the docket number found in brackets in the heading of this document.