## Appendix A

## FDA Supporting Material form Submission

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[**Notices**]
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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.

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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

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Register, FDA is issuing a draft guidance for industry entitled ``PET Drug Applications--Content and Format for NDA's and ANDA's,'' which is intended to assist manufacturers that submit applications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\.



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.

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

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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.

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\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)).

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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.

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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 Sec. 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 Sec. 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 Sec. 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.

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\3\Under Sec. 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.

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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.)

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\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.

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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 (Sec. 314.161(a)(1)).

FDA reviewed its records and, under Sec. 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



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

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\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.

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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 Sec. 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 (Sec. 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 Sec. 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)



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 Sec. 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 (Sec. 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 Sec. 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'' (Sec. 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.

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\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.

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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 Sec. 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



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 Sec. 314.94(a)(12) for ANDA's, Sec. 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 Sec. 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.

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\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.

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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.

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## 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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## Appendix B
## Evaluation of Diagnostic Tests
### Table II--/Fourfold table demonstrating "blind" comparison with "gold

**standard"**
**(Source: CMA Journal 1981)**

| | | **Gold standard** | | |
|---|---|---|---|---|
| | | Patient has the disease | Patient does *not have* the disease | |
| Test result (conclusion drawn from the results of the test) | Positive: Patient appears *to have* the disease | True Positive a | False Positive b | a + b |
| | Negative: Patient appears *to not have* the disease | c False Negative | d True Negative | c + d |
| | | a + c | b + d | a + b + c + d |

Stable properties:
a/(a + c) = sensitivity
d/(b + d) + specificity

Frequency-dependent properties:
a/(a + b) = positive predictive value*
d/(c + d) = negative predictive value
(a + d)/(a + b + c + d) = accuracy
(a + c)/(a + b + c + d) = prevalence

*Positive predictive value can be calculated other ways too. One of them uses Bayes' theorem:

$$\frac{\text{(prevalence)(sensitivity)}}{\text{(prevalence)(sensitivity)} + \text{(1 – prevalence)(1 – specificity)}}$$

**Appendix C**
**MCAC Proposed Guidelines for Evaluating Diagnostic Tests**

When they are asked to evaluate diagnostic tests, panels can apply criteria that are similar to those used for other health interventions that come before the Medicare

Coverage Advisory Committee. The panels will need to determine whether the evidence is adequate to conclude that the diagnostic test improves outcomes and, if the evidence is adequate, to classify the magnitude of the health benefit, when a test is used for a specific purpose.

When more than one application of the test is under consideration, the panels will need to evaluate each application. Although this document refers to diagnostic tests, it is important to recognize that tests have four principal uses in clinical settings, and that the comments in this document refer to all four uses.

> *Screening*: screening refers to the use of a test to detect either asymptomatic disease or a predisposition to disease (i.e., a risk factor such as elevated blood pressure or high blood cholesterol). Typically, the pre-test probability of disease (i.e., the prevalence or probability of disease in the population to be screened) is very low in such individuals. The purpose of screening is either to take action to prevent disease by modifying a risk factor, or to detect and treat disease early. In both cases, screening is presumed to be advantageous because early treatment of disease, or modification of a risk factor, improves health outcomes.
>
> *Diagnosis*: a test is used to make a diagnosis when symptoms, abnormalities on physical examination, or other evidence suggests but does not prove that a disease is present. Making a correct diagnosis improves health outcomes by leading to better clinical NCDs about further testing and/or treatment.
>
> *Staging:* a test is used to stage a disease when the diagnosis is known but the extent of disease is not known. Staging is particularly important when stage of disease, as well as the diagnosis itself, influences management. For example, an early stage cancer might be treated surgically, while the same cancer at a more advanced stage might be treated with chemotherapy alone.
>
> *Monitoring*: in a patient known to have a health condition, a test is used to monitor the disease course or the effect of therapy. A monitoring test helps to evaluate the success of treatment and the need for additional testing or treatment.

Although an effective diagnostic test reduces the morbidity and mortality of disease by guiding clinical NCDs, direct proof of effectiveness is usually unavailable. Few studies have directly measured the effects of a diagnostic or screening test on health outcomes (studies of occult blood testing for colon cancer represent one such exception). Typical studies that evaluate the effectiveness of diagnostic, screening, or monitoring tests focus either on technical characteristics (e.g., does a new radiographic test produce higher resolution images) or effects on accuracy (does it distinguish between patients with and without a disease better than another test).

An improvement in the technical performance of a test can lead to improved diagnostic accuracy. For example, a higher resolution imaging study is more likely to distinguish between normal and abnormal anatomic structures, since it is able to delineate both types of structures more clearly. It may seem self-evident that improved technical characteristics would routinely lead to greater test accuracy and clinical utility, but that is not always the case. Often the factor that limits the ability

of a test to distinguish between diseased and non-diseased, or between a person at high risk for disease and a person at average risk, is not the technical performance of the test. Sometimes the indicator that we are trying to measure (e.g., the risk factor) is only imperfectly correlated with the health condition, and improved measurement of the indicator will not lead to greater accuracy. Occasionally technical performance can improve in one respect but worsen in another; for example, MRI scans have higher resolution than most CT scans. Thus MRI scans were initially believed to be superior to CT scans for most indications. However, because CT scans are better able to distinguish certain tissue types, they proved to be better at detecting some abnormalities than the higher-resolution MRI scans. Thus improvements in aspects of technical performance are not sufficient to establish improved diagnostic accuracy.

When good quality studies directly measure how the use of a diagnostic test affects health outcomes, the panel can easily determine that the evidence is adequate and draw conclusions about the magnitude of the health benefits. But when the best studies only measure the accuracy of the test itself, the panels will have to determine whether the evidence is adequate to conclude that the test improves the accuracy of diagnosis or staging of disease *and* that the improvement in accuracy leads to better health outcomes.

We suggest that panels evaluating diagnostic test answer the following question:

> **Is the evidence adequate to conclude that the use of the diagnostic test leads to a clinically significant improvement in health outcomes?**

If *direct* evidence linking the use of the test to health outcomes is not available, the panels should answer the following questions, which collectively determine whether there is convincing *indirect* evidence that the test will lead to better health outcomes:

**Question 1:** ***Is the evidence adequate to determine that the use of the test provides more accurate diagnostic information?***

The definition of "more accurate" is crucial. The standard measures of accuracy are **sensitivity** (probability of a positive test result in a patient with a disease or risk factor or other health condition) and **specificity** (the probability of a negative test result in a patient who does not have the disease). Ideally a new test would increase *both* sensitivity and specificity. Often that is not the case. A test that has a higher sensitivity is not unambiguously more accurate than an alternative test unless its specificity is at least as great. For most diagnostic tests, a change in the definition of an abnormal result will change the sensitivity, but improved sensitivity is obtained at the cost of worsened specificity, and vice versa. For example, if the diagnosis of diabetes is made on the basis of a fasting blood sugar, the use of a lower blood sugar level to define diabetes results in greater sensitivity and lowered specificity when compared to a diagnostic threshold at a higher blood glucose level. By choosing a different threshold, it is possible to change sensitivity without changing the test. Thus, if only sensitivity (or specificity) were considered, the same test might appear more accurate solely because the definition of an abnormal test result was changed.

The foregoing discussion leads to the following definition of "more accurate:" A more accurate test is not only more sensitive (or specific); it *has a higher sensitivity for a given level of specificity* when compared to another test. At a minimum, then, to conclude that one test is more accurate than another, its sensitivity (or specificity) is must be higher while its specificity (or sensitivity) is the same or better than the alternative test or diagnostic strategy.[1]

In deciding whether one test is more accurate than a second, established test, the panels will find the following steps helpful.

***Step 1: Evaluate the quality of studies of test performance***

The panel should first address the quality of the studies that are used to determine test accuracy. In assessing the quality of studies, panels might first consider the characteristics of an "ideal" study of test accuracy and compare the existing studies to the ideal. "Ideal" and "typical" studies of a screening, diagnostic, or monitoring test differ in these ways:

| Ideal study | Usual study | Effect of Usual Study |
|---|---|---|
| The study subjects are consecutive patients seen in a typical clinical setting with a chief complaint. | Subjects selected because they had the diagnostic gold standard. | Overestimates sensitivity and underestimates specificity |
| All patients who get the index test also get the reference test | Patients with negative results on the index test often don't get the diagnostic gold standard | Overestimates sensitivity and underestimates specificity |
| The person who interprets the index test is blinded to all other information | The person who interprets the index knows the clinical history and the results of the diagnostic gold standard. | Overestimates sensitivity and specificity. |
| The person who interprets the reference test is blinded to all other information | The person who interprets the diagnostic gold standard knows the clinical history and the results of the index test. | Overestimates sensitivity and specificity. |
| The reference test is a valid measure of the disease state | The diagnostic gold standard imperfectly measures the disease state. | The measured test performance could either be worse or better than the true performance. |

*The **reference test** is a test that is considered the "gold standard," i.e., a test that is used to define the disease. Tests commonly used as reference tests are coronary angiography, for coronary artery disease, and histopathology, for cancer. Reference

test can be interpreted more broadly to mean any method that is considered the definite basis for determining whether a disease or risk factor is truly present. The panels will need to decide whether the results of studies that fall short of the ideal are likely to be due to bias, or whether their limitations are sufficiently minor that it is possible to draw conclusions about the accuracy of the test.

***Step 2: Evaluate the possibility that the two tests are complementary***

The sensitivity and specificity of a new test can be the same as – or even worse than – the sensitivity and specificity of an established comparison test, yet still provide valuable information. It can add value if it provides complementary information. In this circumstance, a combination of the two tests leads to more accurate distinction between patients with and without the disease (or risk factor) than either test individually. The information is likely to be complementary if the other test or tests detect other features of the disease (for example, one test measures a physiological phenomenon while the other is an imaging test that detects structural abnormalities). A direct comparison between strategies using the two tests and those using only the standard test can be made by studying patients who receive both tests as well as the reference test (or any direct measure of whether disease is actually present). The appendix describes how such a study can be used to determine whether the combined testing strategy improves the accuracy of diagnosis.

**Question 2:** ***If the test improves accuracy, is the evidence adequate to conclude that the improved accuracy will lead to better health outcomes?***

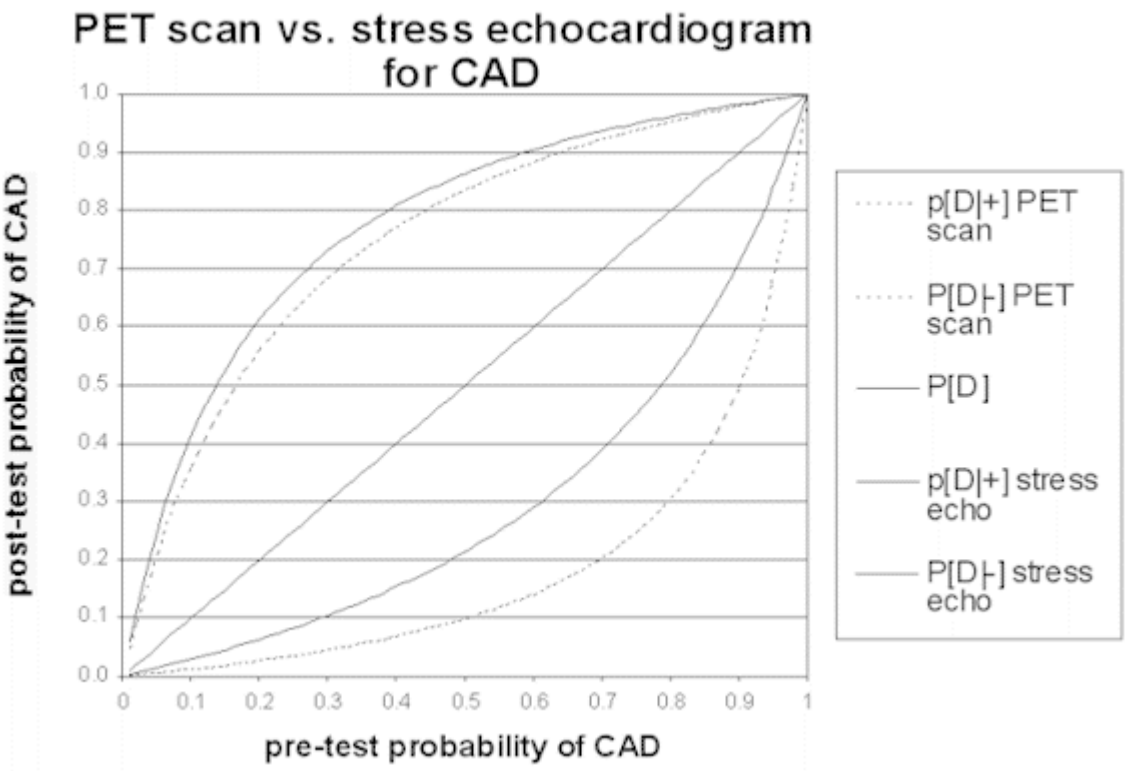
To determine whether a difference in test accuracy would lead to important improvements in health outcomes, the panels may find the following steps helpful.

***Step 1: Calculate the post-test probability of disease***

The purpose of testing is to reduce uncertainty about the presence of a disease or risk factor, or about the extent of a previously diagnosed disease. The pre-test probability of disease is the probability of disease before the test has been performed, based upon history, physical examination, and preliminary diagnostic tests. The pre-test probability is often used interchangeably with the term "disease prevalence," but the two terms are only equivalent when prevalence and pre-test probability are based on the same population (i.e, adjusted for history and other information).

The post-test probability is the probability of disease after learning the test results. A test result should only change patient management if it changes the probability of disease. Bayes' theorem is the formal approach used to calculate the post-test probability. Application of Bayes' theorem in this context requires the sensitivity and specificity of the test and the pre-test probability of disease. Generally, tests alter probability the most (i.e., in comparison to the pre-test probability) when the pre-test probability is intermediate (i.e., not near a probability of either 0 or 1). Conversely, tests alter probability the least when the pre-test probability is close to zero or close to 1.0. If the patient's symptoms, abnormalities on physical examination, and other evidence strongly suggest that the patient has the disease in question (i.e., the pre-test probability of disease is high), unless a test is extremely

sensitive the patient is likely to have the disease even if the test result is negative, and should be managed accordingly. Similarly, if the pre-test risk of disease is very low, the probability of disease in a patient with a positive test result remains very low, unless the test is extremely specific (i.e., rarely produces false-positive results). The accompanying graph of post-test probability for two tests illustrates this point. Panels may find these graphs helpful in interpreting the possible impact of a difference in test performance.




The same principles apply to the use of testing to stage disease or to monitor the effect of treatment. In these situations, the uncertainty is not about the diagnosis, but the test is needed to reduce uncertainty about the current status of the disease. Learning more about stage or response to treatment is important insofar as it will influence management options – for example, disease progression while on one treatment will often lead to a change in therapies, or cessation of a potentially toxic therapy. A false-negative staging test result (i.e., one that implies the disease is more limited than it really is) may lead to treatment that is both ineffective and harmful. In some situations, a false-positive staging test result can have even more harmful consequences; the physician could withhold potentially curative treatment if he or she interprets the staging test as indicating that cure is not possible, dooming a patient to die of a disease that could have been treated effectively.

***Step 2: Evaluate the potential impact on management when tests differ in the post-test probability***

:

In the absence of direct evidence of the effects of a test on health outcomes, it will sometimes be possible to conclude with great confidence that improved accuracy will lead to better outcomes. This is particularly likely to be true when the treatment or management strategy is effective for patients with the disease, but poses risks or discomfort that would not be acceptable when administered to patients who do not have the disease. Then, improved accuracy leads to effective treatment for more people who truly have the disease, and helps avoid unnecessary treatment in people who would not benefit from it. Thus, although the evidence that diagnostic tests for cancer and for heart disease alter health outcomes is largely indirect, it is also compelling. For these categories of disease, there is often strong evidence that treatments with significant adverse consequences are effective when used appropriately. Panels will need to judge whether the test leads to better patient management by increasing the rate at which patients with disease receive appropriate treatment and the rate at which patients who do not have the disease avoid unnecessary treatment.

*If* management changes, the improvement in health outcomes should be large enough that the panel believes it is clinically significant. A small increase in accuracy can lead to substantial improvements in health outcomes if treatment is highly effective. Improved accuracy is of little consequence, however, if treatment is either ineffective, so there is little benefit to patients with the disease, or very safe, so there is little harm to patients without the disease. Then improved accuracy is unlikely to lead to improved health outcomes or even to influence clinical NCDs.

Under exceptional circumstances, prognostic information, even if it did not affect a treatment decision, could be considered to improve health outcomes. The panel should be alert for circumstances in which patients would be likely to value the prognostic information enough to significantly alter their well-being.

**Summary**

The recommended approach for evaluating diagnostic tests is as follows:

- Review, when available, high quality studies that provide *direct* evidence that test results improve health outcomes.

- If there is no high quality *direct* evidence, evaluate the *indirect* evidence as follows:

    Decide whether studies of test accuracy are sufficiently free of bias to permit conclusions about the accuracy of the test under consideration, in comparison either to another test or another screening, diagnostic, or staging strategy

    Evaluate the potential impact of improved accuracy (or complementary information) on health outcomes. Evaluating the effect of test accuracy on post-test probability is one part of this step. The other part is deciding whether the change in patient management that results from the test will improve health outcomes. Improved outcomes are likely to occur when the management strategy is effective in patients with the disease and does not benefit those without the disease. A test can

also improve health outcomes when the treatment poses significant risk, so that it is very important to avoid unnecessary treatment.

---

[1]The more technical expression of this condition is that a more accurate test is one whose receiver operating characteristic (ROC) curve is above and to the left of the ROC curve for the alternative test.

**APPENDIX: THE COMPLEMENTARY VALUE OF COMBINED TESTING**

To test the hypothesis that two tests are complementary, several approaches are possible. The best way is a study in which a series of patients receive both tests as well as the reference test. The analysis compares the sensitivity of the second test in two groups of patients: those with a negative result on the first test and those with a positive result, as shown in the table.

| | **Test 1 results positive** | | **Test 1 results negative** | |
|---|---|---|---|---|
| Test 2 results | Reference standard positive | Reference standard negative | Reference standard positive | Reference standard negative |
| Positive | A | | A' | |
| Negative | B | | B' | |
| Totals | A+B | | A'+B' | |

If the sensitivity of Test 2 when test 1 is negative (A'/[A'+B']) is greater than zero, Test 2 is able to detect patients that Test 1 cannot, and the two tests are complementary. If, on the other hand, the sensitivity of Test 2 is zero when Test 1 is negative, Test 2 is unable to detect patients that Test 1 would miss, and it is of minimal additional value.

Many studies of two tests do not provide the information in this table. However, the studies may still provide useful data that reflect what is in the table. The best way to think about using two tests is to consider them as a sequence of tests, in which the post-test probability after the first test becomes the pre-test probability for the second test. Suppose that the test under consideration is the second test in the sequence. It would add information when compared to the established test alone under two circumstances:

- The first test in the sequence is positive, and the post-test probability after a positive result on the second test in the sequence is greater than the post-test probability after the first test.

- The first test in the sequence is negative, and the post-test probability after a negative result on the second test in the sequence is lower than the post-test probability after the first test.

Arguments that consist largely of inductive reasoning (based upon a different physiological basis for Test 2) are much weaker than empirical evidence.

## Need for additional research

As noted above, the quality of studies that have been performed to evaluate FDG PET could be significantly improved. In all of the clinical conditions for which Medicare will now provide coverage, and for the remaining oncologic and other clinical uses, there is still a need for additional high quality clinical studies. HCFA is aware that there is limited public and private funding available for clinical research, particularly for studies that evaluate the clinical utility of promising technologies that emerge from basic research. For this reason, Medicare has recently implemented a policy for paying the routine costs for patients in clinical trials. The policy is aimed at increasing participation of Medicare patients in diagnostic and therapeutic trials, and well-designed evaluations of PET would be likely to qualify for coverage under this policy. For technologies of unique public health importance, HCFA will consider paying for the cost of experimental interventions in the context of clinical trials. This has been done in the past for several NIH-sponsored clinical trials that will provide critical evidence for developing HCFA coverage policy.

HCFA encourages the PET community to consult with experts in the evaluation of diagnostic technology in designing studies that will improve the empirical information available to clinicians and patients who use PET. HCFA staff is also available to meet with scientists and clinicians involved in the development of novel technologies in order to provide general advice on study design. We have initiated discussion with the National Cancer Institute to explore the possibility of collaborating with the PET community on these high priority studies, and look forward to continuing those discussions. More consistent conduct of these studies will be the most efficient way for Medicare to continue to expand coverage for novel beneficial technologies in a time frame that better matches the pace at which they are being developed.

## Consideration of remaining indications

The current request for broad coverage received on July 10, 2000 is now considered closed by virtue of this coverage decision. Our review of all evidence submitted and additional evidence gathered supports the conclusion that the request for broad coverage is denied. Within that broad coverage request, we did find sufficient evidence to support coverage for the conditions described earlier in this document. The use of PET for clinical indications not addressed in this decision memo or previous Medicare coverage policies will remain non-covered. We encourage the requesters or others to submit new separate coverage requests for use of FDG PET in any additional clinical conditions that they believe would meet the coverage standards described in this document.