Guidance

Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs

DRAFT GUIDANCE

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

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Clinical/Medical

Guidance

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I. INTRODUCTION

This guidance summarizes the investigational new drug application (IND) process for unapproved positron emission tomography (PET) drugs, makes recommendations on how to submit an IND, provides advice on investigational PET drug access options, and describes the process for requesting permission to charge for an investigational PET drug. This guidance does not describe all the considerations relevant to an Expanded Access submission or to an IND Request to Charge submission. For details about these processes, we encourage sponsors to review the applicable regulations and advice available on the FDA Web site,[2] and consult the review division, if necessary.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. PET Drugs

PET drugs are diagnostic radiopharmaceuticals that, following injection into humans, produce signals for medical images through the emission of a positron. The dual photons that emerge from the positron emission are detected by PET scanning devices to form images that map the location of the radiopharmaceutical within the body. Most PET drugs are produced using cyclotrons at locations in close proximity to the facility that performs the PET scanning. Due to

[1] This guidance has been prepared by the Division of Medical Imaging Products in the Center for Drug Evaluation and Research (CDER) at FDA.

[2] The regulations may be found by placing the key words *expanded access* into the search box at www.fda.gov or at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/ InvestigationalNewDrugINDApplication/ucm172492.htm.

the short half-lives of PET drugs, most of the drugs are injected intravenously into patients or investigational subjects within a few minutes or hours of production.

Throughout this document, *clinical use* refers to administration of the PET drug to patients as a component of their clinical care with no intent to study the safety or effectiveness of the drug in any systematic way. This is to be differentiated from *investigational use* and *research use* of PET drugs. *Investigational use* refers to the administration of PET drugs to subjects under an IND to establish the safety and/or effectiveness of a new use of the drug to support an application for approval of that use. *Research use* refers to administration of PET drugs to human research subjects typically under a Radioactive Drug Research Committee (RDRC) application to obtain basic information regarding the metabolism, physiology, pathophysiology or biochemistry of the PET drug. Such administration is *not* intended for immediate therapeutic, diagnostic purposes, nor to determine the safety and effectiveness of the drug.

The Food and Drug Administration Modernization Act of 1997[3] (the Modernization Act) provided that certain unapproved PET drugs would not be considered adulterated until the new current good manufacturing practice (CGMP) regulations for PET drugs (21 CFR part 212) took effect, if the production facility maintained compliance with United States Pharmacopeia (USP) monograph expectations for the specific drug, as well as compliance with the USP chapter 823 standards.[4] As of September 1, 2011, the following PET drugs had USP monographs:

- ammonia N13 injection
- carbon monoxide C11
- fludeoxyglucose F18 injection
- fluorodopa F18 injection
- flumazenil C11 injection
- mespiperone C11 injection
- methionine C11 injection
- raclopride C11 injection
- rubidium chloride Rb82 injection
- sodium acetate C11 injection
- sodium fluoride F18 injection
- water O15 injection

B. IND

An IND is a request for authorization from the FDA (1) to administer an investigational drug or biological product to humans, (2) to obtain exemption from the premarketing approval requirements that are otherwise applicable, and (3) to lawfully ship the investigational drug or product for the purpose of conducting clinical investigations.[5] FDA has developed several guidance documents to assist in the development of an IND.[6] These documents describe

[3] Public Law 105-115.

[4] See section 501(a)(2)(C) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 351(a)(2)(C)), added by section 121(b) of the Modernization Act. Section 121(b) also provided that section 501(a)(2)(C) would sunset two years after the date on which the Secretary of Health and Human Services established PET CGMP regulations, which is December 12, 2011.

[5] See 21 CFR 312.1.

[6] The IND guidances are available on the Internet at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/ InvestigationalNewDrugINDApplication/default.htm.

considerations for a *traditional* IND[7] as well as those for special situations (e.g., emergency IND and treatment IND).

An IND is submitted by a sponsor. The sponsor is the person or entity who takes responsibility for and initiates a clinical investigation. The sponsor can be a company, a private or academic organization, or an individual. A sponsor-investigator is an individual who both initiates and conducts a clinical investigation and under whose immediate direction the investigational drug is being administered or dispensed. For administrative reasons, only one individual or entity should be designated as an IND sponsor.

Upon receipt of the IND by the FDA, an IND number is assigned. The FDA reviewing division sends a letter to the sponsor providing notification of the IND number assigned, date of receipt of the original application, address where future submissions to the IND should be sent, and the name and telephone number of a contact person at FDA to whom questions about the application should be directed. Clinical investigations cannot be initiated until 30 days after the date of receipt of the IND by FDA unless FDA provides earlier notification that the studies can begin.[8] If FDA identifies deficiencies during the 30-day review period, the deficiencies will be communicated to the sponsor. Certain deficiencies may warrant FDA placing a clinical hold upon the investigations until the deficiencies are addressed.[9]

III. SUMMARY OF APPLICATION SUBMISSION REQUIREMENTS

Section 121(c)(1)(A) of the Modernization Act directed FDA to establish appropriate approval procedures and CGMP requirements for PET drugs. Section 121(c)(2)(A) of the Modernization Act specified that PET drug manufacturers and compounders would be required to submit applications for approval within 24 months of the establishment of such procedures and requirements. The publication of the final rule on CGMP for PET drugs on December 10, 2009,[10] triggered the requirement that all producers of PET drugs submit applications by December 12, 2011. Until June 12, 2012, FDA does not intend to take enforcement action against a PET facility currently producing PET drugs for clinical use for a failure to submit a new drug application (NDA) by December 12, 2011, provided that the facility complies with all other FDA requirements, including current good manufacturing practices (CGMPs). FDA will not exercise enforcement discretion after June 12, 2012. If producers of certain PET drugs submit an NDA or abbreviated new drug application (ANDA), FDA will not object if clinical use of these drugs continues during the application review period. However, all PET producers must be operating under an approved NDA or ANDA, or effective IND, by December 12, 2015.[11]

FDA recognizes that it may be very difficult to develop NDAs for certain PET drugs that are currently in clinical use. This guidance specifies that expanded access is available for these types

[7] IND for an investigational use of a drug under circumstances that do not satisfy criteria for special types of INDs, such as expanded access, exploratory, emergency, or treatment INDs.
[8] 21 CFR 312.40(b).
[9] See 21 CFR 312.42.
[10] See the final rule, "Current Good Manufacturing Practice for Positron Emission Tomography" (74 FR 65409).
[11] Section 121(c)(2)(A) of the Modernization Act.

of drugs. See section VI.D for a description of when FDA would consider it difficult to develop an NDA for certain PET drugs.

Section 121(c)(2)(B) of the Modernization Act states that nothing in the Modernization Act exempts PET producers from the requirement to have an IND. FDA has not been enforcing the IND requirements pending completion of the CGMP regulations and approval procedures. Now that the CGMP regulations and approval procedures have been completed, our expectations regarding INDs for PET drugs under investigational use are as follows:

- If the PET drug used in the clinical trial is being made at a facility for which manufacturing data have been submitted in an NDA or ANDA for the PET drug, then FDA does not intend to object to use of the PET drug in a clinical trial without an IND until December 12, 2015, if this and the requirements in 21 CFR 312.2 (other than being lawfully marketed) are met (see 21 CFR 312.2(b)) However, if significant manufacturing deficiencies are found during the NDA/ANDA review, or during inspection of the facility the PET drug is sourced from, FDA may notify the sponsor that the PET drug may no longer be used in clinical trials.

- After December 12, 2015, investigational use of a PET drug must be covered by an IND unless it is exempt from all of the IND requirements.

FDA has prepared two tables that summarize the application and IND submission requirements for PET drugs. These tables are contained in the guidance on *FDA Regulation of PET Drug Products, Questions and Answers*.[12]

In the discussion that follows, we provide guidance on the different uses of PET drugs; which, if any, IND is appropriate; and what to submit to FDA.

- *Investigational use*: Submit traditional IND (see section V)

- *Clinical use when an NDA or ANDA cannot be submitted* (see section VI.B): Submit expanded access IND

- *Research use*: No IND required if reviewed by RDRC (see section IV)

Section IV.A describes when certain research on a PET drug can be performed subject to approval of an RDRC. In such a case, an IND is unnecessary. In some cases, performing certain studies or trials of a PET drug may be exempt from IND and RDRC requirements. Criteria for IND exemption are described in section IV.B.

[12] The guidances referenced in this document are available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page. When finalized, this guidance will represent FDA's current thinking on this topic.

Sections V.A and V.B describe the logistics of submitting a traditional IND for investigational use of a PET drug. In some cases, described in section VI, an *expanded access* IND can be used for continued clinical use of a drug for which an NDA or ANDA is not feasible.[13] Finally, section VII contains information about when a sponsor can charge for a PET drug under an IND.

IV. WHEN AN IND IS *NOT* NEEDED FOR A PET DRUG

A. Conducting Research Using PET Drugs Under RDRC Rather Than Under an IND

FDA regulations at 21 CFR 361.1 describe conditions under which radioactive drugs (including PET drugs) can be used for certain research without an IND because they are generally recognized as safe and effective for those uses, subject to approval by an RDRC.[14] RDRC approval to conduct research is based upon a determination that the research is basic science research, and not research that is intended for immediate therapeutic, diagnostic, or similar purposes, or to determine the safety and effectiveness of the radioactive drug or biological product for such purposes (i.e., the research cannot constitute a clinical trial for the product). The regulations list three additional requirements for human subject research that may be conducted under an RDRC:

1. The research must be approved by an RDRC that is approved by FDA (21 CFR 361.1(b)(1) and (c)(4)).

2. The dose to be administered must be known not to cause any clinically detectable pharmacological effect in humans (21 CFR 361.1(b)(2)).

3. The total amount of radiation to be administered as part of the study must be the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study, and must be within specified limits (21 CFR 361.1(b)(3)).

Only RDRCs approved by the FDA are authorized to review and approve the proposed basic research studies. If the basic science research study is approved by an RDRC, the research can be conducted without the submission of an IND. An IND is necessary if the proposed research project does not meet the criteria for review and approval by an RDRC[15] or criteria for IND exemption (see section IV.B).[16]

FDA anticipates that most investigational uses of PET drugs will be conducted under an IND because these studies will likely involve assessments of the drug's safety and/or efficacy and not meet all the criteria for RDRC approval. An IND is often the preferred route, since the goal of research conducted under RDRC oversight is very limited, while clinical research performed

[13] FDA regulations pertaining to expanded access and charging are found on the Internet at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/ InvestigationalNewDrugINDApplication/ucm172492.htm.

[14] See also the guidance for industry and researchers on *The Radioactive Drug Research Committee: Human Research Without an Investigational New Drug Application* (the RDRC guidance).

[15] See 21 CFR 361.1.

[16] See also 21 CFR 312.2(b).

under an IND may have many goals, including a goal of providing patient access to the investigational PET drug.

B. Exemption From an IND

In considering the need for an IND, sponsors should recognize that some studies or trials are exempt from an IND if the investigational drug is approved for a clinical indication. A clinical investigation of a drug is exempt from the IND requirements if all of the criteria for an exemption in 21 CFR 312.2(b) are met:

- The drug product is lawfully marketed in the United States.
- There is no intent to report the investigation to FDA as a well-controlled study in support of a new indication and no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product.[17]
- The investigation is conducted in compliance with the requirements for review by an Institutional Review Board (IRB)[18] and with the requirements for informed consent.[19]
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the sponsor or investigator does not intend to promote or commercialize the drug product).

When considering the possible exemption of an investigation from the IND submission requirement based on the fact that the drug is approved, investigators should be aware that FDA approval of a PET drug or submission of an NDA or ANDA for a PET drug allows manufacturing of the drug only at the approved manufacturing facility. For example, by December 2010, FDA had approved three NDAs for fludeoxyglucose F18 injection with manufacturing performed at the specific facilities cited within the NDA. Fludeoxyglucose F18 drugs produced at other facilities are unapproved drugs that generally may only be used under an IND, except as described below.

Because sponsors need only submit NDAs or ANDAs by June 12, 2012, as stated previously:

[17] See 21 CFR 312.2(b)(1)(iii).
[18] See 21 CFR 56.
[19] See 21 CFR 50.

- If the PET drug used in the clinical trial is being made at a facility for which manufacturing data have been submitted in an NDA or ANDA for the PET drug, then FDA does not intend to object to use of the PET drug in a clinical trial without an IND until December 12, 2015, if this and the requirements in 21 CFR 312.2 (other than being legally marketed) are met (see 21 CFR 312.2(b)). However, if significant manufacturing deficiencies are found during the NDA/ANDA review, or during inspection of the facility the PET drug is sourced from, FDA may notify the sponsor that the PET drug may no longer be used in clinical trials.

- After December 12, 2015, investigational use of a PET drug must be covered by an IND unless it is exempt from all of the IND requirements.

For example, if PET producer A submits an ANDA to make fludeoxyglucose F18 at PET centers B, C, and D, FDA does not intend to object to investigational use of fludeoxyglucose F18 sourced from PET producer A and made at PET centers B, C, and D without an IND. However, an IND would be required for investigational use of fludeoxyglucose F18 sourced from PET producer A and made at PET center E, which is not proposed as a facility in the ANDA, or from PET producer X, if X has not submitted an ANDA or NDA for fludeoxyglucose F18 .

V. HOW TO SUBMIT A TRADITIONAL IND FOR INVESTIGATIONAL USE

A. What Information Should Be Submitted in a Traditional IND?

The minimum contents for a clinical trial IND submission are described in 21 CFR 312.23 and summarized below (for Expanded Access submission, see Appendix A). We also request that you include a Certification of Compliance (Form FDA 3674) to address the requirements of the ClinicalTrials.gov Data Bank. At a minimum, an IND should contain:

- A cover sheet (Form FDA-1571) with the requisite contact information and other form-specified commitments.
- A table of contents.
- An introductory statement and description of the general investigational plan.[20]
- A copy of the Investigator's Brochure to be provided to each site investigator. An Investigator's Brochure is not required for sponsor-investigators.[21]
- A copy of the clinical protocol (including a description of objectives, eligibility criteria, total enrollment size, time and nature of evaluations, major endpoints and analyses, identification of the study safety monitor, any "stopping rules" for toxicity,[22] description of mass/radiation dose and administration route, screening for pregnancy, and plan for development of final report).[23]

[20] See 21 CFR 312.23(a)(3).
[21] See 21 CFR 312.23(a)(5).
[22] See the guidance for industry on *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products,* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074980.pdf.
[23] See 21 CFR 312.23(a)(10)(ii) and 21 CFR 312.23(a)(11).

- Chemistry, manufacturing, and control information for the investigational PET drug (for details see section VI.E).
- Pharmacology and toxicology information that support the sponsor's conclusion that it is reasonably safe to conduct the proposed clinical investigation.
- A summary of any previous clinical experience with the investigational PET drug.
- Sufficient data/information to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs.

An IND can be submitted in a paper or electronic format.[24] If submitted in a paper format, at least three copies of the application should be supplied.

Copies of Form FDA 1572 (Statement of Investigator) with its attachments can be sent by a sponsor-investigator to satisfy Form 1571, box 12, item 6 b-d. Information can be supplied in the form of attachments (such as curriculum vitae) rather than entering that information directly onto the form, but this information should be so noted under the relevant section numbers. The Form 1572 is not required for submission with an IND.

If an IND is submitted to study any PET drug in a clinical trial, including any one of the 12 drugs listed with bullets in section II, the clinical trial use of the drug may not begin until the IND goes into effect. However, FDA does not intend to object to the use of a PET drug in a clinical trial before an IND takes effect under the circumstances described in sections III and IV.B above when an NDA or ANDA has been submitted for the drug and the manufacturing facility at which it is made, or takes effect under expanded access as described in section VI.E. As noted in section II.B, an IND goes into effect 30 days after FDA receives the IND, unless FDA notifies the sponsor that the proposed clinical trial is subject to a clinical hold. In some situations, FDA may permit an IND to go into effect and the clinical trial to begin fewer than 30 days following the date FDA receives the IND submission. In these situations, FDA will notify the sponsor when the IND is in effect. Sponsors should describe within the IND submission any special considerations for the desired trial initiation timeline.

For phase 1 clinical trial submissions, sponsors should refer to the guidance for industry on *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products*.[25]

For phase 2 and phase 3 clinical trial submissions, sponsors should refer to guidance for industry on *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information.*[26]

B. Where Should the IND Be Submitted?

For clinical investigations of PET drugs in diagnostic imaging, the IND should be submitted to:

[24] Information regarding the electronic submission process is available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm.

[25] Available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[26] Available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Food and Drug Administration
Central Document Room
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

Telephone inquiries regarding the submission of INDs for PET drugs can be directed to the Division of Medical Imaging Products, project management staff, at 301-796-2050.

In some situations, investigational PET drugs can be used in diagnostic imaging agent assessments for investigational therapeutic drugs. In these situations, when both investigational drugs are submitted under one IND, the IND generally will be routed to and managed by the FDA review division responsible for the investigational therapeutic drug.

VI. EXPANDED ACCESS FOR CLINICAL USE OF CERTAIN PET DRUGS

A. Definition of *Expanded Access*

Expanded access refers to a range of IND mechanisms intended to provide access to investigational drugs outside of traditional clinical investigations.[27] See sections VI.B and VI.D for appropriate use of expanded access as a mechanism for continuing clinical use of a PET drug.

When an investigational drug is made available under an expanded access IND, the primary purpose is to diagnose, monitor, or treat a patient's disease or condition, rather than characterize the safety and/or effectiveness of the investigational drug.[28] There are situations in which expanded access can be used as an alternative to traditional clinical investigations (as described in section VI.C) to make investigational PET drugs available to certain patients.

The aim of expanded access is to facilitate the availability of the investigational new drug to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor or treat the patient's disease or condition. An *Expanded Access Submission* refers to a type of IND submission (either an original IND or a protocol submitted to an existing IND) that contains all the information for FDA to assess the appropriateness of the proposed treatment use. In the context of PET drugs, *treatment* refers to clinical use for diagnostic purposes.

B. General Criteria for Expanded Access

To permit expanded access to an investigational drug, FDA must determine that the following general criteria are met in accordance with 21 CFR 312.305, as well as additional criteria that are specific to each of the IND categories:[29]

[27] See 21 CFR part 312, subpart I.
[28] See 21 CFR 312.300.
[29] For additional criteria applicable to each category of an expanded access IND, see 21 CFR 312.310 for an individual patient IND, 21 CFR 312.315 for an intermediate-size population use, and 21 CFR 312.320 for a treatment IND.

1. The Patient or Patients To Be Treated Have a Serious or Immediately Life-Threatening Disease or Condition.

An *immediately life-threatening disease or condition* means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.[30] A *serious disease or condition* means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning.[31] FDA recognizes that a serious health risk may represent a serious condition, including when a patient does not have a clinically evident active serious condition or disease. Therefore, even in the absence of an active, clinically evident serious condition, a disease or condition may be considered serious if it is likely that the disease would progress to a serious condition if left untreated. So use of an investigational PET drug to help detect a serious disease or condition in the situation where the patient does not actively manifest the disease or condition would still be considered use for a serious disease or condition.

2. There Is No Comparable or Satisfactory Alternative Therapy to Diagnose, Monitor, or Treat the Disease or Condition.

FDA has generally recognized the term *alternative therapy* to refer to any therapy that is specified in the approved labeling of regulated products, with only rare exceptions.[32] In making an expanded access submission for an investigational PET drug, the sponsor should explain why the PET imaging diagnostic information cannot be attained with comparable or satisfactory alternatives that use approved drugs. FDA recognizes that the diagnostic evaluation of patients could involve multiple test methods that use approved drugs and that these tests commonly provide incremental information without any single test establishing a clinical diagnosis. In this context, the unique capabilities from the use of a PET drug (e.g., the ability to assess metabolic activity or identify specific receptors within organs) might support the finding that there is "no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition."[33] For example, magnetic resonance imaging (MRI) or Computerized Tomography (CT) with an approved contrast agent might provide considerable central nervous system (CNS) structural information, but a PET drug might provide important CNS blood flow or receptor-binding site information that cannot be obtained with MRI or CT. In that setting, MRI or CT would not represent a comparable or satisfactory alternative diagnostic test to PET imaging because of the different nature of the information provided by PET imaging.

3. The Potential Patient Benefit Justifies the Potential Risks of the Treatment Use, and Those Potential Risks Are Not Unreasonable in the Context of the Disease or Condition to Be Treated.

[30] See 21 CFR 312.300.
[31] See 21 CFR 312.300.
[32] Additional information is available in the FDA guidance for industry on *Available Therapy*, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
[33] See 21 CFR 312.305(a)(1).

FDA makes this determination based on the available evidence to support the treatment use, the size and nature of the population that will be exposed, and the relative seriousness of the disease or condition. PET drugs can be used to assist in the diagnosis of multiple serious conditions, such as coronary artery disease or malignancies. In these situations, we anticipate that the potential risks of the diagnostic use will not prove unreasonable in most patient populations. The administered mass doses of PET drugs are generally low enough to lack pharmacologic activity and to produce relatively large safety margins (i.e., the doses are often several fold lower than the no observed adverse effect level (NOAEL) doses tested in preclinical studies). The radiation-absorbed dose from the radionuclide (e.g., F18, N13) is also generally low.[34] In some patient populations, such as children and pregnant women,[35] the risks of exposure to radioactivity raise special concerns and applicants should specifically justify the unique risks to these more vulnerable populations.

4. Providing the Investigational Drug for the Requested Use Will Not Interfere With the Initiation, Conduct, or Completion of Clinical Investigations That Could Support Marketing Approval of the Expanded Access Use or Otherwise Compromise the Potential Development of the Expanded Access Use.

For the types of expanded access INDs that will be used for PET drugs, FDA does not expect that interference with development of the drug for marketing approval will usually be an issue. As discussed in more detail in section VI.D, FDA anticipates that expanded access INDs for PET drugs will generally be used in situations in which it is not feasible to develop the PET drug for marketing approval.

C. Types of Expanded Access Appropriate for PET Drugs

The regulations provide for three categories of expanded access INDs based on the size of the population in which the drug will be used:

- individual patients (including emergency use), where each submission is limited to a single patient (21 CFR 312.310)
- an intermediate-size patient population, where the submission supports administration of the drug to more than one patient but not the widespread use of the drug (21 CFR 312.315)
- widespread use under a treatment IND or treatment protocol (21 CFR 312.320)

An individual patient IND or protocol can be used if the PET drug is only used very infrequently. As with all categories of expanded access, an individual patient IND or protocol typically must

[34] See Einstein, AJ, Moser, KW, Thompson, RC, Cerqueira, MD, Henzlova, MJ. Radiation Dose to Patients from Cardiac Diagnostic Imaging. *Circulation* 2007; 116:1290-1305.

[35] See 21 CFR 361.1 and also the guidance for industry, *The Radioactive Drug Research Committee: Human Research Without An Investigational New Drug Application*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM163892.pdf.

be submitted before use of the drug.[36] But, in the case of an emergency that requires the patient to be treated before a written submission can be made, FDA may authorize the use to begin without a written submission and use of the drug may begin upon verbal authorization from FDA before use.[37]

If a sponsor anticipates that there will be more than sporadic, isolated use of an investigational PET drug, FDA recommends use of an intermediate-size population IND. Under this type of IND, FDA typically authorizes use prospectively in a prespecified number of patients (e.g., 10 to 20). If that number is reached, the sponsor can then ask FDA to authorize use in additional patients. There are three possible intermediate-size population INDs for an investigational drug — (1) for a drug being actively developed, (2) for a drug that cannot be developed because the disease (or the use) is rare (see section VI.D below concerning when the latter should be used), and (3) for an approved or related drug that is not available through marketing channels.[38]

To be able to provide access under a treatment IND or treatment protocol, a sponsor must be actively pursuing marketing approval of the drug, and clinical trials adequate to support the marketing application must have been completed or must be ongoing.[39] Because of these expectations, FDA anticipates that the treatment IND or treatment protocol category of expanded access will have limited utility as a pathway to make investigational PET drugs available to patients. FDA anticipates that expanded access INDs for PET drugs will generally be individual patient or intermediate-size patient population INDs.

D. Use of Expanded Access INDs for PET Drugs in Situations for Which NDAs or ANDAs Are Not Feasible

When the CGMP regulations take effect in December 2011, FDA expects that an NDA or ANDA will have been submitted for the clinical use of PET drugs. However, FDA recognizes that for certain PET drugs in clinical use, NDA or ANDA submissions will not be feasible at this time because of difficulties associated with commercial development of these products. FDA also recognizes that there will still be clinical situations in which these PET drugs will continue to be needed. In these situations, if there is no satisfactory alternative diagnostic imaging drug for the clinical setting in which the PET drug is used (see discussion in section VI.B.2), and the other applicable criteria are met, an individual patient expanded access submission or an intermediate-size population access submission for a drug that is not being developed may be used to provide access to the PET drug.

FDA generally prefers use of an intermediate-size access IND, where appropriate, because it permits FDA to prospectively authorize multiple uses of the PET drug. If the drug is not being developed, this type of access submission must explain, among other things, why the drug cannot be developed and under what circumstances, if any, the drug could be developed.[40]

[36] See 21 CFR 312.305(d).
[37] See 21 CFR 312.310(d).
[38] See 21 CFR 312.315(a).
[39] See 21 CFR 312.320.
[40] See 21 CFR 312.315.

In general, a PET drug will be considered difficult to develop if all of the following conditions exist:

- Use of the PET drug by the institution producing the PET drug is limited to use within that institution.
- The isotope properties (e.g., very short half-life) and nature of use (e.g., use is limited to a small niche population) of the PET drug preclude commercialization.
- There is no commercially available formulation of the PET drug.

Expanded access is generally not the appropriate mechanism to make a PET drug available to patients if there is an approved NDA for the same formulation and the NDA holder does not have marketing exclusivity, even if the drug cannot be made commercially available outside the NDA holder's institution. In this situation, FDA expects submission of ANDAs for the drug, using the approved NDA product as the reference product.

Four of the 12 drugs with a USP monograph listed in see section II (ammonia N13, fludeoxyglucose F18, sodium fluoride F18, and rubidium chloride Rb82) have been approved by the FDA for production at certain facilities. FDA believes that expanded access is generally not an appropriate mechanism to make these drugs available to patients for indications that are the same as the reference drug. Instead, FDA expects submission of an ANDA or NDA for those PET drugs. However, an intermediate-size expanded access IND may be appropriate to continue clinical use of a PET drug for an indication that differs from the reference drug.

FDA recognizes that the clinical use of the remaining eight drugs with a USP monograph may prove so uncommon that the usage may not justify the submission of an NDA. Accordingly, sponsors might choose to make these drugs available to patients under an expanded access submission as outlined above or under an IND submission that contains a clinical trial protocol.

In addition to the 12 drugs with a USP monograph, other PET drugs might be eligible for expanded access. For these other PET drugs, sponsors should be particularly aware of the requirement that an expanded access submission include chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the drug (i.e., justification for adequate production quality).[41]

Once an expanded access IND or treatment protocol is submitted, FDA does not intend to object to the *continued* clinical use during the 30-day IND review period (given IRB approval) because FDA understands that the prior clinical use will have been supported by compliance with USP standards, which continue as standards for INDs. If FDA detects important safety concerns during the 30-day review period, the sponsor will be notified. If the treatment protocol or expanded access IND is for a *new* clinical use (no prior clinical use of the drug manufactured at a particular facility for a particular indication), then clinical use of the drug may not begin until 30 days after FDA receives the treatment protocol or expanded access IND, or on earlier notification by FDA.[42]

[41] See 21 CFR 312.305.

[42] See 21 CFR 312.305(d).

E. Content of an Expanded Access Submission

Appendix A lists the requirements for the content of an Expanded Access IND submission.[43] In this section, we discuss how to meet the submission requirements for some of the required content in an Expanded Access IND submission for a PET drug.

In some situations, a sponsor may not have direct access to all the information called for in a complete expanded access submission. For example, the investigational PET drug's manufacturing information might be contained within an existing IND. In this situation, the expanded access IND submission could contain a *right of reference* letter. The right of reference letter comes from the sponsor of the existing IND and is addressed to the sponsor of the expanded access submission. This letter should provide permission for the FDA to access the existing IND manufacturing information to support the expanded access IND submission. This letter should then be included within the expanded access IND submission.

1. Is the Chemistry, Manufacturing, and Controls (CMC) Information Adequate to Ensure Identity, Strength, Purity, and Quality of the Investigational PET Drug?

FDA's regulations at 21 CFR 312.305(b)(2)(vi) require that an expanded access submission include sufficient CMC information to ensure the proper identification, strength, quality, and purity of the drug.

Sponsors can reference an official compendium to provide certain CMC information (e.g., general methods, monograph standard) for an investigational drug substance or drug product, when applicable. Reference to drug master files (DMFs) or other existing INDs or NDAs, with an authorization letter from the holder, sponsor, or applicant, can also be used to provide CMC information in support of the IND submission.[44]

For an IND submission for a traditional clinical trial, the amount of information submitted can vary with the phase of the investigation, the proposed duration of the investigation, and the amount of information otherwise available from referenced sources. Similarly, for an expanded access IND submission, the amount of CMC information required depends on the size of the population to be treated.

FDA recommends that the following information, which is considered CMC safety information (information needed to assess safe use of a drug product), be submitted in the original IND submission. If during the course of investigation any CMC changes are made that could affect safety, those changes should be submitted in an IND amendment. The CMC information submitted can be formatted in Common Technical Document (CTD) format.[45]

[43] See 21 CFR 312.305(b).
[44] See 21 CFR 312.23(b).
[45] See "Module 3 – Quality" in the International Conference on Harmonization guidance for industry, *M2 eCTD: Electronic Common Technical Document Specification*, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

- **Drug Substance** (entire radioactive molecule including the radionuclide), **Reference Standard and Intermediate**

    a. General Information – include name; structure; and relevant physical, chemical, and biological properties.

    b. Manufacture

        i. Manufacturers – include name, address, and responsibility of each facility involved in the manufacturing or testing of radionuclide, nonradioactive intermediate (precursor), and radioactive drug substance.
        ii. Description of Manufacturing Process and Process Controls – include flow diagram(s) and description of the synthesis and production processes for the radionuclide, nonradioactive intermediate (precursor) from starting material, and the radioactive drug substance. Include the batch formula and the equipment used for the synthesis of radioactive drug substance.
        iii. Control of Materials – include controls for starting material(s), reagents, solvents, and other auxiliary materials used in the synthesis of radionuclide, nonradioactive intermediate, and the radioactive drug substance.
        iv. Controls of Critical Steps and Intermediates – include suitable controls for intermediates isolated during the synthesis of nonradioactive intermediate (precursor) and controls employed during the radioactive drug substance synthesis.

    c. Characterization

        i. Radioactive drug substance - include structure characterization data and analysis for the radioactive drug substance using a well-characterized single lot of nonradioactive reference standard; provide a comparison of chromatographic mobility of the radioactive drug substance and the nonradioactive reference standard.
        ii. Nonradioactive reference standard (surrogate) – include structure characterization data, method of synthesis and purity information for the reference standard lot. If applicable, include information on stereoisomeric purity and potential for isomerism.
        iii. Nonradioactive intermediate (precursor) – include structure characterization data and analysis, method of synthesis of the reference standard lot, and information on stereoisomeric purity and potential for isomerism.
        iv. Controls for Nonradioactive Reference Standard – include a listing of all the tests performed (e.g., description, identity, assay, impurities, residual solvents) and the tentative acceptance criteria. A list should be provided for the testing performed by the sponsor and, if different, by the drug product manufacturer. Test results and analytical data (e.g., spectra, chromatograms) from batch release of representative clinical trial

materials should also be provided initially and when any changes are made in the specification. Information on the analytical procedures should be provided.

v. Reference Standards or Materials
   - Nonradioactive drug substance reference standard – include information on manufacturer, manufacturing process used, structure characterization data on the lot with interpretation, information on purity of the lot, batch analysis data on primary and working reference standard lot, container closure, storage and stability information on reference standard.
   - Information on nonradioactive intermediate (precursor) reference standard (if applicable)

vi. Information on Container Closure System Used for the Nonradioactive Intermediate (Precursor).

vii. Information on Stability and Storage of the Nonradioactive Intermediate.

- **Drug Product**

  a. Description and Composition of the PET Drug Product – include list of all the components, their quality grade (e.g., USP, National Formulary (NF)), and their amounts on a per unit basis. Indicate the function of each component. Provide a description of any diluent used and the container closure used.

  b. Manufacture
     i. Manufacturers – include name, address, and responsibility of each facility involved in the manufacturing or testing of the PET drug product.
     ii. Description of Manufacturing Process and Process Controls – include flow diagram(s) and description of the drug product manufacturing process, including the batch formula used.
     iii. Controls – include description of any controls used during the drug product manufacture.

- **Control of Excipients** – include information on specification, quality grade, and acceptance procedures for excipients.

- **Control of Drug Product** - include a listing of all the tests performed (e.g., appearance, radiochemical identity and purity, assay, radionuclidic identity, pH, specific activity, impurities, residual solvents) and the tentative acceptance criteria. Test results and analytical data (e.g., spectra, chromatograms) from batch release of representative clinical trial materials should also be provided initially and when any changes are made in the specification. Information on the analytical procedures should be provided. Information on impurities and their control should be discussed.

- **Reference Standards or Materials** – include information on any unique reference materials used in the drug product analyses.

- **Container Closure System** – include name and address of the manufacturer and specifications for the container closure system used for the PET drug product. If a reference is made to a drug master file (DMF), include an authorization letter from the DMF holder. For packaging components (e.g., glass, elastomeric stopper), compliance with appropriate compendial standards should be stated.

- **Stability** – include stability data to support the expiration dating period. Stability should be performed at the upper range of the radioactive concentration produced.

- **Labeling** – include a copy of the labels that are affixed to the drug product (e.g., Vial, lead shielding). In addition to the relevant identifying and other information, the label for the investigational product should contain the statement "Caution: New Drug – Limited by Federal (or United States) law to investigational use" in accordance with 21 CFR 312.6(a).

- **Environmental Assessments –** FDA believes that the PET drug products use small quantity of materials and will qualify for a categorical exclusion. Sponsors may request categorical exclusion from performance of an environmental assessment in accordance with 21 CFR 25.31(e).

FDA recommends that the sponsor carefully assess any changes in the drug substance and the drug product manufacturing process (or drug product formulation) that are used while the IND is in effect to determine whether the changes can directly or indirectly affect the safety or efficacy of the PET drug product. For changes with significant potential to affect the safety of the product, an information amendment must be submitted that describes the changes and contains relevant information at a level of detail sufficient for an adequate review and assessment.[46] When appropriate, this amendment should include data from tests on the drug substance and/or drug product produced from the previous manufacturing process and the changed manufacturing process to evaluate product equivalency, quality, and safety. In addition, when analytical data from tests on the drug substance and/or drug product demonstrate that the materials manufactured before and after are not comparable, sponsors should perform additional qualification and/or bridging studies to support the safety of the material to be used in the investigational studies.

2. Is Pharmacology and Toxicology Information Adequate to Conclude That the Investigational PET Drug Is Reasonably Safe at the Dose and Duration Proposed for Expanded Access Use?[47]

Because PET drugs are usually administered at microdose levels, an expanded access IND submission for these drugs will generally call for limited pharmacology and toxicology information. The submission should contain a description of the drug's receptor binding characteristics and the mechanism of action, and should provide evidence of an adequate safety margin (i.e., the proposed clinical doses are several fold lower than the no observed adverse

[46] See 21 CFR 312.31.
[47] 21 CFR 312.305(b)(2)(vii).

effect level (NOAEL) doses tested in preclinical studies). These data could be obtained from the sponsor's own work, from publicly available clinical and nonclinical data, or by right of reference to proprietary data. In some situations, a sponsor may not have direct access to all the information called for in a complete expanded access IND submission. For example, the investigational PET drug's pharmacology and toxicology information might be contained within an existing IND. In this situation, the expanded access IND submission could contain a right of reference letter (See introduction to section VI.E).

3. Is There Clinical Evidence Available to Support Use of an Investigational PET Drug (Preliminary Clinical Evidence of Effectiveness or Plausible Pharmacologic Effect)?

The expanded access submission should contain clinical data and information that provides at least preliminary evidence that the PET drug is effective for the expanded access use and does not present an unreasonable risk of harm in the type of population in which it is anticipated to be used. A range of clinical data and information might be relied on, including data from clinical trials, clinical pharmacology data (pharmacodynamic and pharmacokinetic findings), clinical experience (e.g., case series), and other evidence from scientific literature.

F. Additional Information for Sponsors of Expanded Access INDs for PET Drugs

Sponsors of expanded access programs must comply with the applicable responsibilities for sponsors set forth in 21 CFR part 312, subpart D.[48] Among other things, sponsors are responsible for providing licensed physicians with the information they need to safely administer the PET drug so as to minimize the drug's risk and maximize its potential benefits, maintaining an effective IND for the expanded access use, maintaining adequate drug disposition records, and submitting to FDA IND safety reports as described in 21 CFR 312.32(c) and IND annual reports as described in 21 CFR 312.33 (when the IND or protocol continues for 1 year or longer).

VII. CHARGING FOR AN INVESTIGATIONAL PET DRUG

FDA's regulations on charging for an investigational drug describe criteria for charging for (1) a drug used in a clinical trial and (2) a drug used under an Expanded Access IND (21 CFR 312.8).

- Charging in a clinical trial

FDA believes that in most cases the cost of an investigational drug in a clinical trial intended to support a marketing application is an ordinary cost of doing business that should be borne by the trial sponsor. The purpose of permitting charging for an investigational drug in a clinical trial is to permit a sponsor to recover the costs of making certain drugs available to study subjects when clinical trials, which would be essential for establishing that a drug is safe or effective or would support a significant change in labeling for an approved drug, could not be conducted without charging because the cost of the drug is an extraordinary cost for the sponsor.[49] A sponsor

[48] 21 CFR 312.305(c)(5).

[49] See CFR 21 312.8(b)(1)(iii).

authorized to charge for its drug in a clinical trial can only recover its direct costs (i.e., the costs that can be specifically and exclusively attributed to providing the drug for the investigational use).[50]

- Charging in an expanded access program

The purpose of permitting cost recovery for expanded access use is to facilitate access to investigational drugs for treatment (diagnostic) use in situations in which a sponsor might not be able to provide such drug absent charging, or to facilitate broader access than would be possible absent charging. In light of this purpose, and because sponsors of intermediate-size patient population expanded access programs and treatment INDs or protocols incur costs in addition to the anticipated and ordinary costs of drug development, such sponsors may recover direct costs as well as indirect administrative costs associated with the expanded access program, including costs associated with monitoring the IND or protocol and complying with IND reporting requirements.[51] However, a sponsor of an individual patient IND or protocol can only recover its direct costs because the administrative costs associated with an IND or protocol for a single patient use are generally negligible.

A. What Information Should Be Included in a Request to Charge Submission?

A *Request to Charge* submission should address all the relevant criteria for the type of IND for which charging is requested[52] (see Appendix B). To facilitate review of the request, we encourage sponsors to prominently highlight that the IND submission is a "Request to Charge" on the cover letter of the submission. A Request to Charge is specific to a protocol and can be submitted as a component of an original IND or as an amendment to an existing IND. A charging request should be mailed to the address cited above (see section V.B). A sponsor may not charge for an investigational drug without prior written authorization from FDA.[53] If the investigational agent is acquired from a PET drug producer, the sponsor of the IND that implements a protocol to administer the drug should submit the request to charge.

B. How Long Can I Charge for the Cost of an Investigational Drug?

For a clinical trial, charging can continue for the length of the clinical trial unless FDA specifies a shorter period.[54] To provide expanded access to an investigational PET drug for treatment use, charging can continue only for 1 year from the time of FDA authorization, unless FDA specifies a shorter period. A sponsor can request that FDA reauthorize charging for additional periods.[55]

[50] See 21 CFR 312.8(d)(1).
[51] See 21 CFR 312.8(d)(2).
[52] See also 21 CFR 312.8.
[53] See 21 CFR 312.8 (a)(3).
[54] See 21 CFR 312.8(b)(2).
[55] See 21 CFR 312.8(c)(4).

Sponsors should be aware that FDA can withdraw authorization to charge at any time if it determines that charging is interfering with the development of a drug for marketing approval or that the criteria for the authorization are no longer being met.[56]

C. Are There Any Special Charging Considerations for Investigational PET Drugs?

Sponsors can submit a Request to Charge coincident with or following an expanded access IND submission or the submission of an IND intended to support a clinical trial. Following review of the Request to Charge, FDA will provide a written authorization or denial of the request.

- Sponsors can charge for an approved drug to be used in a clinical trial (e.g., trial of a new use of an approved drug or for use of an approved drug as an active control) without permission from FDA if the approved drug is obtained from an entity not affiliated with the sponsor.

- Some clinical trials can use an investigational PET drug that has an approved reference drug (ammonia N13, fludeoxyglucose F18, sodium fluoride F18, and rubidium chloride Rb82 reference drugs) to evaluate an indication that differs from the reference drug. If the investigational PET drug production site is not listed in the approved application for the reference drug, a Request to Charge can be submitted, but FDA believes that demonstrating extraordinary cost (Appendix B) will be difficult to fulfill because an approved production alternative exists.

[56] See 21 CFR 312.8(a)(4).

APPENDIX A: INFORMATION TO INCLUDE IN AN EXPANDED ACCESS SUBMISSION

FDA regulations at 21 CFR 312.305(b)(1) states that an expanded access submission is required for each category of expanded access, and that submission may be a new IND or a protocol amendment to an existing IND. The items listed below must be included in the expanded access submission for a PET drug, and its mailing cover must be plainly marked "EXPANDED ACCESS SUBMISSION" (§ 312.305(b)). Expanded access submission for PET drugs should be mailed to the IND mailing address previously identified in section V.B. FDA's review is greatly facilitated by sponsors providing a title and number for reference purposes. The submission must contain:

- A cover sheet (completed Form FDA 1571).

- The following information, which typically may be contained in a protocol:

    - The rationale for the intended use of the drug, including a list of available diagnostic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available diagnostic options.[57]

    - The criteria for patient selection or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments of the disease or condition.[58]

    - The method of administration of the drug, dose, radiation-absorbed dose, and any plan for repeat administration.[59]

    - Clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.[60]

    - The facility where the drug will be produced.[61]

- Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug.[62]

- Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for expanded access use.[63]

[57] See 21 CFR 312.305(b)(2)(ii).
[58] See 21 CFR 312.305(b)(2)(iii).
[59] See 21 CFR 312.305(b)(2)(iv).
[60] See 21 CFR 312.305(b)(2)(viii).
[61] See 21 CFR 312.305(b)(2)(v).
[62] See 21 CFR 312.305(b)(2)(vi).
[63] See 21 CFR 312.305(b)(2)(vii).

- Information to support a finding that:
    - The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose or monitor the disease or condition.[64]
    - The potential patient benefit justifies the potential risks of the diagnostic use and those potential risks are not unreasonable in the context of the disease or condition to be evaluated.[65]
    - Provision of the investigational drug for the requested use will not interfere with the initiation, conduct or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.[66]

If the Expanded Access Submission is for an individual patient, the following additional information must be supplied:

- Information demonstrating that the physician determined that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition.[67]
- Information to support a finding that the patient cannot obtain the drug under another IND or protocol.[68]

If the Expanded Access Submission is for an intermediate-size population (i.e., for more than one patient, but for a smaller population than the large populations typical of treatment INDs or protocols), the following additional information must be supplied:

- State whether or not the investigational drug is under development for marketing approval. If the drug is not being developed, describe the reasons for lack of development, and the circumstances under which the drug could be developed. If the drug is under development, describe why the proposed access patients are unable to participate in a clinical trial of the drug, and circumstances under which the sponsor would conduct a clinical trial in those patients. For example, identify whether the trials are closed to enrollment or the trial sites are geographically inaccessible.[69]
- Provide at least preliminary clinical evidence of the effectiveness of the drug or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable diagnostic option in the anticipated patient population.[70]

[64] See 21 CFR 312.305(a).
[65] See 21 CFR 312.305(a)(2).
[66] See 21 CFR 312.305(a)(3).
[67] See 21 CFR 312.310(a)(1).
[68] See 21 CFR 312.310(a)(2).
[69] See 21 CFR 312.315(c).
[70] See 21 CFR 312.315(b)(2).

- Describe the patient population to be treated, including the planned size of the patient population.[71]

[71] See 21 CFR 312.315(c).

APPENDIX B: CRITERIA FOR EVALUATING A REQUEST TO CHARGE IND SUBMISSION

When considering submission of a Request to Charge IND submission, the sponsor should first determine whether the request involves charging within a clinical trial or charging for expanded access to the investigational drug for treatment use. If the charging is for expanded access, then the sponsor should identify which of the three categories is applicable to the access program, as follows:

- Individual patient
- Intermediate-size population
- Treatment IND or Treatment Protocol

For requests to charge for all types of expanded access, a sponsor must provide reasonable assurance that charging will not interfere with developing the drug for marketing.[72] To obtain authorization to charge under a Treatment IND or Treatment Protocol access program, that assurance must include specific information.[73] For example, the sponsor must provide evidence of sufficient enrollment in any ongoing clinical trial(s) needed for marketing approval to reasonably assure FDA that the trial(s) will be successfully completed as planned (21 CFR 312.8). In general, we anticipate that few, if any, sponsors will submit a Request to Charge under a Treatment IND or Treatment Protocol for an investigational PET drug, and we do not address this topic further in this guidance. Please refer to § 312.8 for additional information.

Listed below is the information that must be submitted in a request to charge for a PET drug in a clinical trial or in an intermediate-size expanded access program.

A. Charging in a clinical trial:

1. Provide evidence that the drug has a potential clinical benefit that, if demonstrated in the clinical investigations, would provide a significant advantage over available products in the diagnosis of a disease or condition.[74]

2. Demonstrate that the data to be obtained from the clinical trial would be essential to establishing that the drug is effective or safe for the purpose of obtaining initial approval of a drug or would support a significant change in the labeling of an approved drug (e.g., new indication, inclusion of comparative safety information).[75]

3. Demonstrate that the clinical trial could not be conducted without charging because the cost of the drug is extraordinary to the sponsor. The cost may be extraordinary due to manufacturing complexity, scarcity of a natural resource, the large quantity of drug

[72] 21 CFR 312.8(c)(1).
[73] 21 CFR 312.8(c)(2).
[74] 21 CFR 312.8(b)(1)(i).
[75] 21 CFR 312.8(b)(1)(ii).

needed (e.g., due to the size or duration of the trial), or some combination of these or other extraordinary circumstances (e.g., resources available to a sponsor).[76]

4. Describe the proposed cost to be charged to a patient and include supporting documentation to show that the calculations represent only *direct* costs. Direct costs include the costs per unit to manufacture the drug (e.g., raw materials, labor, and non-reusable supplies and equipment used to manufacture the quantity of drug needed for the use for which charging is authorized) or costs to acquire the drug from another manufacturing source, and direct costs to ship and handle (e.g., store) the drug. Only direct costs may be considered for charging in a clinical trial.[77]

5. Include a statement that an independent certified public accountant has reviewed and approved the cost calculations.[78]

B. Charging for expanded access to investigational drug for treatment use (intermediate-size patient population access):

Provide reasonable assurance that charging will not interfere with developing the drug for marketing approval.[79] For example, for certain PET drugs, it might not be feasible to conduct trials of sufficient size to support an NDA due to (a) the limited use and (b) on-site preparation or limited region of distribution because of the relatively short half-life of the radionuclide. If the expanded access program is limited to a defined number of patients, FDA asks that applicants verify that the charging is also limited to this number of patients. In addition, the charging request must:

1. Describe the proposed cost to be charged to a patient and include supporting documentation to show the calculation is consistent with the requirements of 21 CFR 312.8(d)(1), and for intermediate-size patient population expanded access, (d)(2).[80] Under 21 CFR 312.8(d)(2), sponsors of intermediate-size patient population expanded access may recover direct costs (as outlined in section A above), as well as the indirect costs associated with monitoring the expanded access IND or protocol, complying with IND reporting requirements,[81] and other administrative costs directly associated with the expanded access IND.

2. Include a statement that an independent certified public accountant has reviewed and approved the cost calculations.[82]

As stated in section VII.B, permission to charge to provide expanded access can be requested yearly (or sooner, if the previous authorization was for a period shorter than one year). Request

[76] 21 CFR 312.8(b)(1)(iii).
[77] 21 CFR 312.8(d).
[78] See 21 CFR 312.8(d)(3).
[79] See 21 CFR 312.8(c)(1).
[80] See 21 CFR 312.8(d)(3).
[81] See 21 CFR 312.8(d)(2).
[82] See 21 CFR 312.8(d)(3).

for reauthorization must satisfy the same requirements that the initial request for charging authorization did.