Guidance

FDA Oversight of PET Drug Products

Questions and Answers

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

December 2012
Procedural

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Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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Guidance[1]

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to help producers of positron emission tomography (PET) drugs meet the requirements for FDA's drug approval process. This guidance provides questions and answers that address nearly all aspects of the drug regulatory process, including application submission, review, compliance with current good manufacturing practices, inspections, registration and listing, and user fees.

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

In 1997, Congress passed the Food and Drug Administration Modernization Act (Public Law 105-115) (the Modernization Act). Section 121 of the Modernization Act directed FDA to establish appropriate approval procedures and Current Good Manufacturing Practices (CGMPs) for PET drugs. The procedures were finalized and an implementation timeline was instituted on December 10, 2009, when FDA published regulations that described the minimum CGMP standards that each PET drug manufacturer is to follow during the production of a PET drug (see 21 CFR part 212) and the guidance *PET Drugs – Current Good Manufacturing Practice (CGMP).*[2] Under the requirements of section 121 of the Modernization Act, within 2 years following that publication date, a new drug application (NDA) or abbreviated new drug

[1] This guidance has been prepared by the PET Drugs Working Group in the Center for Drug Evaluation and Research (CDER) at FDA.

[2] The regulation, CGMP guidance, and supportive information, including historical documents, are available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm. 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.

application (ANDA) must be submitted for any PET drug marketed for clinical use in the United States.

Recognizing that many PET drug producers are unfamiliar with the drug regulatory process, particularly the drug application and review process, FDA issued the guidance *PET Drug Applications – Content and Format for NDAs and ANDAs,* and held a public meeting in March 2011 to assist applicants in preparing NDAs and ANDAs for the three most commonly used PET drugs. Numerous questions have been raised since that public meeting on all aspects of PET regulation. This guidance is being issued to respond to the questions that have been submitted to date, and it will be revised periodically to respond to additional questions that have been submitted and are expected to be submitted in the future.

In addition to this guidance, FDA has issued two other guidances, *Media Fills for Validation of Aseptic Preparations for PET Drugs* and *Investigational New Drug Applications for Positron Emission Typography (PET) Drugs.*

III. QUESTIONS AND ANSWERS

A. General Questions

1. Application Submission

Q1: Will FDA grant an extension for filing applications?

FDA does not intend to disrupt existing clinical use of PET drugs as long as appropriate submissions are made and producers of PET drugs are moving to comply with regulatory requirements. In December 2011, FDA announced that 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 an 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. Therefore, if a facility wishes to continue to produce PET drugs for clinical use after June 12, 2012, they must have submitted an NDA or ANDA by that date, or be producing the drugs under an investigational new drug application (IND). PET facilities who are unable to submit an NDA or ANDA by June 12, 2012, or operate under an IND must find a new supplier who has submitted an NDA or ANDA. All PET producers must be operating under an approved NDA or ANDA, or effective IND, by December 12, 2015.

See Appendix A for FDA's current views of how PET drug production can continue under various application submission scenarios.

Q2: If we do not file an ANDA by December 12, 2011, is it true we have to wait 3 full years before we can submit those applications?

No. You may submit the application at any time, but you will be at risk of enforcement action if you continue to produce PET drugs for clinical use after June 12, 2012, without having submitted an NDA, ANDA, or in some cases, an IND. Applicants can continue producing PET drugs for clinical use while the NDA, ANDA, or IND is under review (see Appendix A).

Q3: Is FDA going to require inspections before PET drug producers can begin making PET radiopharmaceuticals?

For PET drugs in clinical use before June 12, 2012, sponsors can continue to produce and use a PET drug if an application for the drug has been submitted by June 12, 2012, and is under review at FDA. The facility does not, however, need to be inspected before production of PET drugs can continue. For example, if you already produce Fludeoxyglucose F18 injection (FDG) for clinical use and have submitted an ANDA for FDG for review, you may continue producing this product and the inspection will be conducted at some time during the review.

No PET drugs for clinical use may be produced after June 12, 2012, unless an NDA or ANDA has been submitted or the drug is being used under an expanded access program. FDA does not intend to exercise enforcement discretion with regard to new PET production facilities that have not been listed in a submitted application. For example, if you have not previously been making FDG, Ammonia N13, or Sodium Fluoride F18 and you wish to bring a new facility on line after June 12, 2012, to make one or more of these drugs, you must first submit an ANDA, and it must be approved before you may market the drug (see Appendices A and B).

Q4: If a manufacturer submits an NDA or ANDA for FDG before June 12, 2012, and the manufacturer wants to (or needs to, due to equipment failure or other cause) upgrade its FDG production method (which might require purchase of another module that uses a different process), can the facility purchase the module, validate the process, and amend the application before the initial inspection of the facility?

If, due to unforeseen circumstances, a change in manufacturing equipment or manufacturing method becomes necessary after an application is submitted but before it is approved, the applicant will need to submit an amendment to the application (see Appendix B). The amendment must contain supporting data and describe all the changes in manufacturing and controls required because of the change (see 21 CFR 314.70). The applicant may also need to submit an assessment of whether the change will affect the identity, strength, purity, or quality of the product described in the original application.

Certain changes (e.g., change in strength, change in composition of the product in relation to the reference listed drug (RLD)) may not be permitted in an ANDA without prior FDA approval of the change (see 21 CFR 314.93).

When an NDA or an ANDA is submitted, the applicant is required in FDA Form 356(h) to provide a complete listing of all the manufacturing, packaging, and control sites for drug substance and drug product and provide information on readiness of each site for inspection (see 21 CFR 314.50(d)(1)). If at the time of inspection the facility is not ready, the application may not be approved. The inspector will be aware of the application and any amendments to it at the time of the inspection.

After an application is approved, 21 CFR part 212 permits an applicant to change equipment provided that it is qualified before use. Under FDA regulations at 21 CFR 314.70, certain changes after approval must be requested in a prior approval supplement (PAS). If a PAS is required and an inspection requested, FDA would seek to perform the inspection as soon as possible.

In preparation for the inspection, an amendment to the application that describes the changes and provides supporting data will need to be submitted. Whenever an amendment is submitted, a field copy (with certification) must also be submitted to inform the inspector of changes (see 21 CFR 314.70(a)(5); see also Appendix B).

Q5: Can we submit an ANDA on CD? If so, do we need to submit a paper copy as back up?

Information on electronic submission on physical media is available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163567.pdf.

It is not necessary to submit a paper copy of the entire submission as a back up. However, if you are submitting on physical media (e.g., a CD or DVD), you should submit a paper FDA Form 356h with original signatures. FDA requires this hard copy document in the unlikely event that the physical media are damaged or corrupted and rendered unreadable. Without the paper document, FDA would not be able to contact the sponsor if the physical media are unreadable.

Q6: Will hybrid applications be accepted?

Yes. CDER's Electronic Submissions Group (ESub Group) will grant waivers for hybrid applications for PET producers. The ESub group will provide instructions to sponsors and advise which forms and templates to use. The ESub group can be contacted at ESub@fda.hhs.gov.

Q7: Is there a way to determine whether a PET producer has submitted an NDA or ANDA for approval or has received approval of an application?

There is no public list of submitted NDAs or ANDAs. FDA cannot publicly disclose the existence of an NDA or ANDA before it is approved unless the applicant has publicly disclosed the existence of the application (see 21 CFR 314.430(b)). Once a product is approved, it is listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). If you intend to purchase PET drugs for commercial use from a producer of those drugs, you should seek assurance from the vendor that they have submitted an application to FDA.

Q8: The guidance *PET Drugs – Content and Format for NDAs and ANDAs,* provides reference to and advice to format an application in the common technical document (CTD) format. The attachments to the guidance, which provide sample formats, are not formatted according to the CTD. What is the correct format for the CTD?

The sample formats have been kept in the old Office of Generic Drug (OGD) format to avoid confusion for the three commonly used drugs (FDG, Ammonia N13, and Sodium Fluoride F18). You may organize the application in the CTD format and keep the chemistry, manufacturing, and controls (CMC) sections (module 3 of the CTD format) as formatted in the CMC attachment. Alternatively, you can organize the application, including CMC, entirely in CTD format. The following FDA guidances provide further information about the CTD format:

- *Submitting Marketing Applications According to the ICH-CTD Format – General Considerations*[3]
- International Conference on Harmonization (ICH) guidance, *M4: Organization of the CTD*
- ICH guidance on *M4Q: The CTD — Quality*

Q9: If the drug substance and the drug product are the same, do applicants have to repeat the information in the two sections of the CTD?

No. You do not have to repeat information if the drug product and substance are the same. You can hyperlink to the section where the information is provided.

Q10: What are the differences between Module 3 for the NDA and ANDA?

[3] This draft guidance, when finalized, will represent FDA's current thinking on this topic.

The modules are the same.

Q11: Would FDA consider an application for FDG for a concentration greater than 300 millicuries (mCi)/milliliter (mL) and perhaps as high as 500 mCi/mL?

FDA has not placed any limit on the strength for the multidose vial. As long as the data support manufacturability and stability of the product at the proposed strength, FDA will consider the application. Be advised that if the proposed strength is not in the mCi/mL range approved for the RLD, a suitability petition or a 505(b)(2)[4] NDA must be submitted (see 21 CFR 314.93). For further information on acceptable ranges, see the guidance *PET Drug Applications – Content and Format for NDAs and ANDAs*.

Q12: Has FDA considered establishing a few different queues for PET applications?

No, FDA has developed internal tracking procedures specifically for PET products, but we do not believe that a different queue is necessary.

Q13: If we use two different synthesizers to make the same product, do we need to submit two NDAs or ANDAs?

You can have two different synthesizers in the same NDA or ANDA as long as the finished product at the end is the same, meaning that the product meets the same set of specifications and the formulation is the same. If the finished product formulation from the two synthesizers is different, two separate applications may need to be submitted. Please contact the Office of Generic Drugs (for an ANDA) or the Office of New Drugs' Division of Medical Imaging Products (for an NDA) to discuss your options. However, in certain cases, a formulation that differs in terms of exception excipients (e.g., a buffer, an antioxidant or a stabilizer) may be submitted within the same ANDA; otherwise, sameness to the RLD must be shown.

Q14: How much does FDA want to see in an application about the parameters and the controls on the cyclotron itself?

Information about the operating parameters for cyclotron operation (e.g., the make of cyclotron used, bombardment times, information on the target, and the target windows), should be submitted. This information may be submitted by a reference to a Type-II Drug Master File (DMF) if the isotope is obtained from outside sources. When buying isotopes from a vendor, appropriate specifications should be established and the vendor should be qualified.

[4] See 21 U.S.C. 355(b)(2) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act).

Q15: Will FDA treat foreign producers who seek to export PET drug products into the United States differently than domestic producers?

No, FDA will not treat foreign PET drug product producers differently than domestic producers.

In addition to other applicable requirements, all foreign drug establishments whose products are imported or offered for import into the United States are required to register their establishment with FDA and list all of their drug products in commercial distribution in the United States. More information on the registration and listing process is available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/ucm2007058.htm.

2. INDs

Q16: Who can sponsor an IND?

INDs can be sponsored by an individual (e.g., a physician), an institution, or a company.

Q17: It is not practical, even for a large clinical center, to submit an ANDA for PET drugs with limited use (e.g., Ammonia N13). Will FDA allow the IND or Radioactive Drug Research Committee (RDRC) pathway?

No. FDA has created a simple regulatory pathway to obtain an approved ANDA for FDG, Ammonia N13, and Sodium Fluoride F18 and does not intend to exempt any PET Center from the requirement to submit an NDA or ANDA to obtain FDA marketing approval to support the clinical use of any of these three products after June 12, 2012. For further information on the pathway, see the guidance *PET Drug Applications – Content and Format for NDAs and ANDAs*.

Q18: Will drugs for which there is a United States Pharmacopoeia (USP) monograph be exempt from submitting an IND?

No. The fact that a drug has a USP monograph does not eliminate the need for an IND, although the drug might be eligible for an expanded access IND if the criteria are met (see the guidance *Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs*).

Q19: What is the definition of *clinical use* in the context of PET drugs?

Clinical use refers to administration of the 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.

Q20: Can research be conducted under an IND for FDG, Ammonia N13, Sodium Fluoride F18, or Rubidium Chloride Rb82?

Yes. Research and/or investigational studies using these drugs should be conducted under an IND if they are being studied for purposes of commercial clinical use (see the guidance *Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs*). Human research using a PET drug may be conducted under the RDRC if it is basic science research and not research that is intended for immediate therapeutic, diagnostic, or similar purposes, or research to determine the safety and effectiveness of the radioactive drug or biological product for such purposes (see the guidance *The Radioactive Drug Research Committee: Human Research Without an Investigational New Drug Application).*

Q21: In submitting the physician-sponsored IND, one of the biggest hurdles is trying to get the necessary preclinical pharmacological and toxicology data to support the submission. Would FDA consider reducing the requirement?

If you have adequate evidence of the PET drug's safe clinical use, you may submit that clinical information to FDA for review and we will determine whether the drug is safe for use within the proposed IND clinical study or studies. The existing clinical information may limit or negate the need for preclinical data. Clinical information from the use of the PET drug's non-radiolabeled ligand may also prove sufficient to limit or negate the need for preclinical data.

For PET drugs that have not been in clinical use, the extent of necessary preclinical data depends on whether the PET drug ligand is a naturally occurring endogenous substance in humans or not. In general, limited or no preclinical data are necessary to support the use of a PET drug that consists of a ligand that is naturally occurring within humans, if the only major *ex vivo* modification is the radiolabeling of the ligand. The extent of preclinical data necessary to support a clinical study or studies under an exploratory IND is more limited than the preclinical data necessary for a traditional IND (see the guidance *Exploratory IND Studies*).

Q22: Many trials for therapeutic drugs are currently being conducted abroad. If a PET drug is used to determine eligibility for the clinical trial abroad, what would FDA need to know about the PET drug when approval is sought under an NDA for the therapeutic drug?

The answer to this question depends on several factors. If the use of the PET drug to determine eligibility is an approved indication in the United States, we would need CMC data to show that the PET drug used in the trial is comparable to the drug that is approved for use in the United States. For example, if a PET drug were to be approved in the United States to identify early Parkinson's or Alzheimer's disease, the foreign trial's PET drug would need to be bioequivalent to the approved drug in the United States.

If the use of the PET drug to determine eligibility is not an approved indication in the United States (e.g., no PET drugs are currently approved to determine whether a patient has early Parkinson's disease or Alzheimer's disease), the safety and efficacy of the PET drug for that use would have to be established and the data submitted within an NDA.

Q23: If a PET drug producer creates a centralized IND (e.g., an IND for multicenter participation and protocol compliance, image acquisition standardization, image output harmonization) to use FDG in biomarker trials and that producer has an ANDA, can the applicant cross-reference the CMC data in the ANDA or must the applicant submit the CMC documentation with the IND?

Cross-referencing to the approved ANDA is acceptable provided that the drug used in the biomarker trials is the drug produced under the ANDA.

Q24: What is FDA's current position regarding the continued use of PET drugs (Fludeoxyglucose F18 Injection, Sodium Fluoride F18 Injection, and Ammonia N13 Injection) in ongoing clinical trials for new uses of these products or to support clinical trials of therapeutic drugs?

FDA's position is 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 without an IND until December 12, 2015, if this and the other requirements in 21 CFR 312.2 are met (see 21 CFR 312.2(b)).

- However, if significant manufacturing deficiencies are found during the NDA or ANDA review, or during inspection of the facility the PET drug is sourced from, FDA may notify the sponsor that the PET drug should 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.

Q25: For a PET drug that has not been approved, what documentation must be provided to support an IND that is already in effect for a therapeutic drug that relies on the PET drug to monitor disease progression or otherwise evaluate the efficacy of the therapeutic drug?

Before December 12, 2015, no CMC documentation for the PET drug needs to be submitted to the IND for the therapeutic drug as long as the PET drug is manufactured at a facility for which supportive manufacturing information has been submitted in an NDA or ANDA. After December 12, 2015, for PET drugs manufactured at facilities that are not named in an approved NDA or ANDA, CMC documentation for the PET drug will need to be submitted to the IND for the therapeutic drug.

Q26 How will an investigator know whether an NDA or ANDA has been submitted and what records should be submitted to document that the PET drug was sourced from a facility named in an NDA or ANDA?

Documentation should be maintained at the trial site where the investigation is being conducted that indicates the number of the NDA or ANDA that contains the CMC data for the facility from which the drug is sourced. Over the next several months, clinical investigators should make sure this documentation is in place for the PET drugs used in their investigations.

Q27: If an approved PET drug is used to determine eligibility for patient entry into an investigational therapeutic trial, will we have to submit an IND for the PET drug and an IND for the therapeutic drug?

No. If the PET drug's use in the investigational trial is not for an approved indication, the sponsor could describe the investigational use of the PET drug in the original IND for the therapeutic drug trial. Two INDs would not be necessary in this situation. The therapeutic drug IND would need to either provide documentation that the PET drug is sourced from a facility with an approved NDA or ANDA, or provide sufficient CMC data to support its use in the trial.

3. ANDAs

Q28: Do I need to use the same manufacturing process as the reference listed drug (RLD)?

No. Within the context of ANDAs, FDA regulations define a drug that is "the same as" a listed drug to mean a generic drug that has the "identical . . . active ingredient(s), dosage form, strength, route of administration, and conditions of use" as its RLD (See 21 CFR

314.92(a)(1)). Differences in the manufacturing processes do not affect whether a product may be submitted and approved under an ANDA.

Q29: Will we need to contact the NDA holder to obtain a sample of the RLD for the comparison testing?

Obtaining the RLD for comparison testing is not necessary. FDA recognizes that for PET products, it may not be possible to do a direct comparison with an RLD product because of the short shelf life of these products.

Q30: A recently approved ANDA for FDG has different inactive ingredients than its RLD, although the drug was found to be bioequivalent. Will this ANDA be considered an RLD?

No, the ANDA would not be identified as an RLD in the Orange Book.

Q31: If an ANDA applicant is referencing an NDA, does the applicant have to perform all of the quality control testing listed in that approved NDA? For example, if the High-Performance Liquid Chromatography (HPLC) and osmolality testing are listed in the RLD NDA, does the ANDA applicant have to include that testing?

No. Each application is reviewed on its own merits. The application must establish the necessary quality standards, tests, and specifications, and demonstrate that the quality standards will be met over the life of the product.

Q32: How would an ANDA applicant be able to demonstrate sameness to the RLD if the composition per batch is not known by the applicant?

The batch size for a generic drug does not have to be the same as the RLD. Only the parameters that are listed in the labeling of the RLD, including strength, which is radioactivity per unit volume at calibration time (e.g., end of synthesis (EOS)), must match (see Q43 for definition of *EOS*). If an RLD lists a range for volume as opposed to the exact volume, the ANDA applicant may also list a range for volume. The strength of each manufactured batch must reside in the approved range of strength for the PET drug.

Q33: When we submit our ANDA, do we need to submit all of the method validation data, or will that be reviewed at the time of FDA inspection?

The method validation data must be submitted in the application and reviewed by the review division for suitability and acceptability (see 21 CFR 314.50(d) and 212.60(c)). The inspector may look at the source data during the inspection.

Q34: If specific standard operating procedures (SOPs) are referenced within the ANDA submission, must the actual SOPs be submitted or may they be made available for review during the inspection? If the SOPs are submitted, can they be amended during the review process?

You do not need to submit SOPs in an application. It is sufficient that the SOPs be made available during the inspection.

Q35: When we are validating instruments, do we need to submit the data or just the results and procedures?

Analytical validation data, not just the results and procedures, should be submitted in the application.

Q36: What specific types of information would be necessary in a post-deadline amendment to allow changes by manufacturers without disruption to supply?

See Appendix B.

Q37: We have ordered software to maintain our SOPs, but the software will not be installed until after we submit the ANDA. Can we submit an amendment to the ANDA with the software information once it is installed?

It is not necessary for applicants to submit their SOPs, or information on the software used to maintain the SOPs, as a part of their ANDA submission. The qualification, maintenance, and changes of software for SOPs will be evaluated during inspection.

Q38: Because some PET production facilities use different synthesizers, the phosphate buffer and amount of ethanol in their ANDA product may differ from the RLD. How can these producers use the same labeling as the NDA?

Any modifications you make to exception excipients when compared to the RLD must be reflected in your labeling, and these are permissible changes to ANDA labeling. See the guidance *PET Drug Applications – Content and Format for NDAs and ANDAs* for permissible changes to the exception ingredients.

Q39: When FDA says that the resulting product should be the same, does it mean all excipients should be identical, meaning exception and non-exception excipients?

Although drugs approved in ANDAs are generally the same as the RLD, there are differences that are permitted. The inactive ingredients for generic drug products for parenteral use are allowed to differ from those of the RLD only in preservative, buffer,

and/or antioxidant. These excipient classes are often referred to as *exception excipients*. The differences in exception excipients must not affect the safety or effectiveness of the generic drug (see 21 CFR 314.94(a)(9)). Additional differences in non-exception excipients are not permitted.

Q40: Is it possible to submit two formulations, where the only difference is the buffer, in one ANDA?

The Office of Generic Drugs (OGD) has agreed to permit an exception to the policy established in the CDER guidance *Variations in Drug Products that May Be Included in a Single ANDA*. Recognizing the special nature of these products, the exception will apply **solely** to applicants seeking approval of PET drug products and will allow an applicant to submit more than one formulation in a single ANDA.

More specifically, OGD will permit an applicant to seek approval of two formulations provided that the two formulations differ only with respect to "exception excipients" (preservative, buffer, antioxidant) as listed at 21 CFR 314.94 (a)(9)(iii). For example, OGD would permit an applicant to seek approval of two formulations, one using a citrate buffer and one using a phosphate buffer in a single ANDA. Applicants must be aware that all relevant CMC, Microbiology, and Labeling information will need to be compiled in the ANDA to support the approval of each formulation.

Once the ANDA is approved, the applicant will also be responsible for maintaining and submitting all postmarketing reports pursuant to 21 CFR 314.80 and 314.81. When submitting any postmarketing reports, the applicants' reports must be able to distinguish between the different formulations.

Q41: Why are the effects of different inactive ingredients on viscosity and specific gravity of the proposed PET drug product relevant for PET products?

When the issue of different inactive ingredients is raised during a review, it is usually because inactive ingredients for parenteral generic drugs may differ from their RLDs only with regard to antioxidants, buffers, or preservatives (see 21 CFR 314.94(a)(9)(iii)). Although differences in inactive ingredients may not affect the properties of the drug product such as viscosity and specific gravity, under FDA regulations the inactive ingredients must be the same, except as noted in Q13 above (see 21 CFR 314.94(a)(9)(iii)).

Q42: How do differences in excipients affect bioequivalence?

If the proposed product is not qualitatively (Q1) and quantitatively (Q2) identical to the RLD, the product's bioequivalence must be demonstrated in accordance with 21 CFR

320.24. FDA will permit a quantitative difference of ± 5 percent while still considering the product to be quantitatively equivalent. For intravenously administered PET drug products, FDA has determined that bioequivalence has been demonstrated in cases where (1) differences in the inactive ingredients are sufficiently small that they will not significantly affect the physical and chemical properties of the drug product, and (2) the inactive ingredients have been previously used in the same or greater quantities in an approved drug product for the same route of administration (see 21 CFR 320.24(b)(6)).

Examples of situations where FDA has determined that a bioequivalence study is not necessary to demonstrate bioequivalence include:

- Presence of or absence of a preservative, buffer, or an antioxidant in the proposed PET drug product, where these ingredients and their amounts have been previously approved in a drug product and their amounts do not significantly affect physical or chemical properties (e.g., specific gravity, viscosity, pH) in relation to the RLD (see 21 CFR 314.94(a)(9)(iii)).

- Presence of or absence of a preservative, buffer, or an antioxidant in the proposed PET drug product, where this change does not affect tonicity (osmolality) of the solution in relation to the RLD or the applicant has established that the change in tonicity will not affect safety or effectiveness of the product (see 21 CFR 314.94(a)(9)(iii)).

To demonstrate bioequivalence under 21 CFR 320.24(b)(6), the application should include a discussion to support that the proposed product differences from the RLD are not likely to affect the safety or efficacy of the product.

Q43: Why is a suitability petition required for a change in the total volume or total radioactivity per vial for a PET drug?

A 505(j) product is required to have the same strength as the RLD (see 21 CFR 314.92(a)(1)). For PET drugs, the radioactive concentration (e.g., mCi/mL) at the calibration time is generally considered to be the strength. Therefore, if this differs, a suitability petition (SP) is needed before submitting a 505(j) application. The strength is compared based on stated strength at the time of calibration, which for a multidose vial of a PET drug is generally at the end of synthesis (EOS). In this guidance, EOS means at the end of manufacturing of the finished drug product. For unit-dose vials, the strength is calibrated to a particular time from the EOS of a unit dose.

The total radioactivity or total volume in a vial is indicative of batch size, and if it does not have an impact on the strength, a suitability petition is not needed. Because large

amounts of radioactivity may have an impact on stability of the finished product, appropriate stability studies are needed to support the stability of the product.

If you need to submit an SP, the petition must be approved before your ANDA is filed. You may refer to approved suitability petitions as the basis for submission of your ANDA. FDA has approved two suitability petitions for FDG (docket numbers FDA 1997-P-0054 and FDA 2010-P-0444). More information on SPs can be found in the guidance *PET Drug Applications – Content and Format for NDAs and ANDAs*.

Q44: Recently there was an NDA approved for sodium fluoride, where the labeling states that the total volume and total radioactivity per vial are variable. Do producers still need to submit a suitability petition if the total content, the total amount of drug in the vial or the total amount of active ingredient in the vial, is different?

No. See the response to question Q43 above.

Q45: If a producer wishes to apply for a concentration higher than 37.5 mCi/mL for Ammonia N13, is it preferable to file a suitability petition or file a 505(b)(2) NDA?

Both routes are available. FDA recently approved SP 2011-P-0337 that asked us to permit the submission of an ANDA containing a concentration of Ammonia N13 up to 260 mCi/mL. Because this suitability petition has been approved, it is easier for an applicant to submit an ANDA that cites this suitability petition. If an applicant wishes to pursue approval of a concentration greater than 260 mCi/mL, a new suitability petition would need to be submitted. Once a suitability petition is approved, then any applicant may use the approved petition as the basis for submitting its ANDA for the change approved in the petition, until an ANDA based on the petition is approved. Once an ANDA is approved for the change permitted in the petition, any applications submitted after the approval date of the first ANDA must cite the approved ANDA as their basis of submission (see 21 CFR 314.94(a)(3)). The suitability petition will no longer be a valid basis for submitting an ANDA once there is a product approval.

For other changes that an applicant wishes to pursue via the SP process, it is likely easier to employ the suitability petition pathway so long as the applicant has an adequate submission timeline in place to allow for the 3- to 4-month period for petition approval. If an applicant does not have sufficient time for the petition process, a 505(b)(2) application may be quicker. Further, applicants should balance any perceived ease of submission with the prospect of user fees (application, yearly product and establishment fees) that would be assessed to 505(b)(2) applicants but are not assessed for ANDA submissions.

Q46: Once an ANDA is submitted, how should FDA be notified of changes in processes or hardware that may be required because of a breakdown in equipment or for some other reason?

See Appendix B.

Q47: In preparing our application, we have been advised that the manufacturer of the sterile empty vial does not have a drug master file (DMF). What information should we provide in our ANDA about the vial?

A DMF is not required for the submission of an ANDA. You may attempt to obtain information for the vial from the vial manufacturer and include this in your ANDA submission. The type of information submitted in the ANDA should include information on type of container material (e.g., type of glass used and information on conformance with USP chapter <661>), type of closure (e.g., type of rubber formulation used, quantitative composition of the formulation, and information that the formulation meets the USP chapter <661>, USP chapter <87>, and USP chapter <88>), and type of crimp seal used. In addition, information you have to assure sterility, apyrogenicity, and container closure integrity should be provided. For more information, please see the guidance *Container Closure Systems for Packaging Human Drugs and Biologics – Chemistry, Manufacturing, and Controls Documentation*.

Q48: What do we have to reference in the ANDA labeling regarding changes in pediatric dosing?

ANDA labeling is required to be identical to the RLD labeling upon which the applicant is basing their ANDA, with certain exceptions. Therefore, an ANDA applicant will only be permitted to incorporate pediatric labeling when the RLD also contains identical pediatric labeling. Applicants who wish to pursue approval of new or additional pediatric indications must conduct the requisite studies to show that the product is safe and effective for use in the pediatric population.

Generally, pediatric studies are conducted in the context of an NDA submission—either a 505(b)(1) or 505(b)(2) submission. However, an applicant may first secure approval of an ANDA and then submit a 505(b)(2) supplement to the approved ANDA. Applicants wishing to pursue approval of additional pediatric labeling should first discuss their proposal with FDA before conducting any studies or submitting any information.

Q49: Considering that PET drugs are distributed outside the normal channels of distribution for drugs, what is the responsibility of academic PET drug producers for printing and distributing a package insert for PET drugs under an approved

application? What is the responsibility for the commercial sector, considering the batch vial does not enter the ordinary channels of distribution?

The package insert is generally supplied by the manufacturer (academic or commercial PET producers) with the product. FDA does not have any requirements related to a package insert for the unit dose dispensed from a released multidose vial and does not regulate the practice of pharmacy. When the manufacturing and pharmacy units are at the same site, the package insert may be retained at the site.

B. Chemistry, Manufacturing, and Controls

1. General

Q50: Does FDA have a document describing good review practice of chemistry?

No. We do not have a document describing the conduct of the chemistry review. However, we do have a number of guidances on CMC that direct the technical review process. We are not planning on issuing a specific document for PET review practices at the present time.

Q51: System suitability requirements in USP chapter <621> suggest that the tailing factor and resolution (or column efficiency, as appropriate) are to be determined on a daily basis. What is FDA's view on system suitability for manufacturing for PET drug products?

The system suitability testing and acceptance criteria should be appropriate for the intended use of the method. The function of the system suitability test is to ensure that the analytical system, including the equipment, is working properly at the time of analysis. The system suitability testing should be performed before the time of analysis on any day of use. The system suitability testing and acceptance criteria are submitted as part of the test method in the application. The review division determines its suitability for the intended use. The inspector may look at the source data during the inspection and verify that system suitability is being performed for each day of use.

For chromatographic systems used in testing, in general, a justification for not using the tailing factor and resolution should be provided. FDA expects that the system suitability at a minimum will consist of injection of three replicates of standard solution in the validated range, where the acceptance criteria should consist of meeting a specified relative standard deviation (RSD) and specified relative retention time. FDA would accept appropriate periodic verification of column efficiency.

Q52: Will FDA accept the use of materials meeting other Agencies' compendial requirements (e.g., European Pharmacopeia), assuming these materials would be declared in the ANDA or NDA, and would be sourced and managed using the local Quality Management System?

If a material (e.g., an excipient) has a USP monograph, generally, the material should meet the USP monograph requirements. However, FDA will accept materials that meet the requirements of other compendial monographs provided that comparability is established and any differences are justified. If there is no USP monograph, then other quality standards may be proposed in the application. If the requirements for other compendia are more robust than USP requirements, FDA would consider the other requirements, when proposed. Many times vendors provide materials that meet requirements of multiple compendial monographs. The quality of these materials should be suitable for the intended final dosage of the drug product.

Q53: Will FDA provide clarity on expectations around Quality by Design (QbD) applicability to PET products?

The QbD approach is optional. We recommend that you refer to the following ICH guidance documents:

- *Q8(R2) Pharmaceutical Development*
- *Q9 Quality Risk Management*
- *Q10 Pharmaceutical Quality System*

If you want to develop a QbD approach to your drug, we recommend that you discuss the details with the review division at the End of Phase-2 meeting or earlier.

Q54: Is there a limit on the volume of PET drug product solution that can be filled in a vial?

Under USP requirements (see General Chapter <1> Injections), if an injection drug product is packaged as a multidose container, the volume in the container is limited to 30 mL. USP also requires that the multidose vials contain a substance or suitable mixture of substances to prevent the growth of microorganisms. Larger volumes may be packaged as *pharmacy bulk packages*, and do not need to contain a substance or substances to prevent the growth of organisms. The pharmacy bulk packages are, however, required to be handled as described in USP chapter <1> as part of the pharmacy operation.

If a PET drug product is produced as a *single-dose container* for use as a single patient dose, its volume as a small-volume injection is limited to 100 mL or less (see USP

General Chapter <1> Injections). Single-dose vial volumes larger than 100 mL are considered to be large-volume intravenous solutions and treated as such.

Q55: A majority of the RLDs list the strength measured at the end of synthesis (EOS). However, most of the drugs can be measured in a dose calibrator after the drug is diluted. Do we have to match the timing of strength measurement exactly so that the activity has to be EOS, or can we measure the activity at the calculation time?

The strength is measured at the EOS of the final formulation. The synthesis is not completed until dilution to produce the finished formulation.

Q56: Under 21 CFR 212.50(f), would an NDA or ANDA submission be deemed adequate with the inclusion of data from production and stability testing of a single batch if full testing is always performed?

Release and stability data for a minimum of three consecutive batches should be submitted for NDAs and ANDAs.

Q57: Please clarify the requirements regarding preparation of two or more units of FDG injection from the same bulk product batch. What quality control sampling plan will be acceptable? What are the restrictions on unit-dose preparation under the ANDA or NDA, and what would be an acceptable quality control sampling plan?

We do not expect testing of samples from each vial when multiple vials are manufactured. Where the test sample would come from depends, to an extent, on the procedure (e.g., automated vs. manual) for filling the multidose vials. We would recommend that you have a procedure in place to describe the subdivision of bulk vials. For PET drugs, the test sample for chemical tests may be obtained from the bulk vial or any of the other vials. The test sample for microbiological testing (sterility and bacteria endotoxin tests) should come from the vial that represents the most likely place for microbiological concerns (e.g., the first vial). Alternatively, if the fill procedure is such that the most likely microbiological contamination vial cannot be clearly identified, random selection should be used.

When unit doses are prepared as part of the pharmacy operation, the test sample to release the batch must be obtained from the final multidose vial (see 21 CFR 212.70(c)).

When unit-dose vials are prepared as part of PET production, the vials should be segregated from the beginning, middle, and end of the fill line and the vial or vials for test sample should be drawn randomly from the segregated vials.

In any case, the sampling procedure used should be described and justified in the application.

Q58: Does FDA have any guidance on what level of reduced testing would be acceptable once a product has undergone process verification?

According to 21 CFR 212.70(c), a PET producer needs to ensure that each batch (or for a product produced in sub-batches, each sub-batch) of a PET drug conforms to specifications. This may involve the following:

- finished-product testing of each batch
- in-process testing of an attribute that is equivalent to finished-product testing of that attribute
- continuous process monitoring of attributes with statistical process controls
- some combination of these approaches

See the guidance *PET Drugs – Current Good Manufacturing Practice (CGMP)* and the preamble to the final rule on CGMPs for PET drugs (74 FR 65409 (December 10, 2009)). Using finished-product testing alone would require testing each batch of a PET drug product for conformance to all specifications. In-process testing might involve use of an online test to determine whether an attribute meets an appropriate acceptance criterion, provided that the relevant attribute does not change during the production of the finished product. Under this scenario, the in-process testing of an attribute could be an adequate substitute for the finished-product testing for that attribute. Continuous process monitoring with statistical process controls involves comprehensive testing of attributes using online monitoring and corresponding adjustments to prevent an upward or downward drift in batch-to-batch measurements of an attribute. Depending on the particular PET drug product and specification, any of the suggested approaches might be acceptable for determining compliance with specifications. When an approach is proposed in the application, it should be justified by data. For approaches other than testing each batch, you might need to provide the results of analyses of a statistically relevant number of batches using alternative controls to justify these alternate approaches. We recommend that the review division be consulted with specific proposals before submission.

Q59: Are applicants required to check the osmolality for every batch of FDG prepared?

When the tonicity of a product is declared in its labeling, the manufacturing process should be appropriately controlled to assure that the osmolality of every batch will conform to labeled osmolality. Osmolality determined during development and

validation might be sufficient to justify not performing testing of every batch. This data should be submitted in the application.

Q60: When is it necessary to dilute final product to meet the concentration specification? Is there a preference to use sterile water, normal saline, or half normal saline?

Normal saline is the most commonly used agent to maintain the isotonicity of the final drug product. However, you may use any of the three named diluents. Justification should be provided if an isotonic product cannot be formulated. In addition, for ANDA products, the diluent used should be the same as the diluent used in the RLD for which the ANDA is being submitted.

Q61: What are FDA's expectations on handling invalid tests and sample size for repeat testing?

Under 21 CFR part 212, it is acceptable to repeat a test that failed the first time if a mistake or error was made in the first attempt to test (i.e., the test was truly invalid). It is not acceptable to simply retest with a new sample because of a failing result; true out-of-specification results must be investigated to determine the cause of the failure to meet the specifications, and corrections must be implemented as appropriate. If a repeat test is appropriate, the sample size depends on what parameter is being tested and should be chosen to ensure the test results are representative of the characteristics of the batch.

Q62: Does FDA have current information about drug master files (DMFs) that might apply to PET?

PET producers should contact their suppliers to determine whether they have a DMF on file with the FDA. FDA does not provide a list of DMFs that are available for reference. For further information about DMFs, see FDA Manual of Policies and Procedures (MAPPs) on DMF files, available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079564.pdf. You can also direct any specific DMF questions to dmfquestion@cder.fda.gov.

Applicants that plan to rely on one or more DMFs should provide a letter of authorization from the DMF holder that gives the ANDA or NDA applicant the right to reference the DMF and for FDA to refer to the DMF in its review of the application in the ANDA or NDA.

Q63: Is notification to the FDA required for replacement of quality control equipment (e.g., gas chromatography (GC), HPLC, or dose calibrator)

Replacement of quality control equipment is managed under the facility's quality system and should be qualified for installation, operation, and performance; therefore, notification is not necessary. However, any change in the analytical method should be reported in accordance with 21 CFR 314.70.

Q64: Does a change in precursor require submission of a supplement?

Yes. The submission should be made under 21 CFR 314.70(b).

Q65: Does a change in container closure system require submission of a supplement?

Yes. The submission should be made under 21 CFR 314.70.

Q66: Does a change in the vendor of inactive ingredients or other auxiliary materials require submission of a supplement?

No, these are reported in the annual report.

2. Stability Testing

Q67: The guidance *PET Drug Applications – Content and Format for NDAs and ANDAs* (the PET drug applications guidance) states that quality control needs to be done for three qualification batches at the highest concentration allowed. Upon how many batches are we required to perform stability testing?

You should conduct stability testing of three batches. For more information, see Attachment I of the PET drug applications guidance titled "Sample Formats – Chemistry, Manufacturing, and Controls (CMC) Section."[5]

Q68: Does stability testing need to be performed on each vial size, for example, 30 mL and 50 mL, if the components are identical?

We recommend that you choose the highest vial size (i.e., the 50 mL size in the example). In some cases, multiple presentations might need to be tested (e.g., if the headspace oxygen-to-surface ratio differs significantly).

Q69: Are we required to perform forced degradation studies with these short shelf life drugs?

[5] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078740.pdf.

For the commonly used PET drugs (e.g., FDG, Ammonia N13, Sodium Fluoride F18), where the storage and other molecular stability characteristics under different conditions have been well defined in the scientific literature, forced degradation studies are not needed when an NDA or ANDA is submitted.

For new PET drugs, the molecular stability and storage conditions under certain stress conditions (e.g., photo-stability, pH dependant stability) might need to be evaluated and described in the application. The need for this testing should be discussed with the review division during product development (e.g., at the End of Phase-2 meeting). During inspection, the inspector may inspect the source data.

Q70: Assuming that product stability is demonstrated, is there any limit to expiry of the product?

The stability data should support the proposed expiration dating period. These data are submitted in the application for which the expiration dating period is approved. The individual batch used may expire earlier than the approved expiration dating period. It is expected that the product will be used before its specified expiry.

3. Sterility Testing

Q71: With respect to sterility testing, what are the requirements for the sample hold time validation and expected storage conditions during hold time?

Sterility testing can begin 30 hours after manufacture without further justification. Delays beyond this time need to be justified and shown to be valid (i.e., that contamination, if present, would result in growth). Samples are to be stored appropriately during the extended hold time; the hot cell might be appropriate for storage.

Q72: Would the air quality requirement still hold if the sterility inoculations were performed in Hungate tubes, which is generally performed within the hot cell environment, not a laminar flow environment?

We recommend that sterility tests be performed in a Class 100 environment so there is no risk of environmental contamination. However, we do understand if the sterility testing has to be performed in a hot cell because of the nature of the product.

C. Current Good Manufacturing Practices

Q73: Are there specific guidances for the qualification of vendors that would guide us in selecting components and establishing standards for vendor compliance?

No guidance on this topic is presently available.

Q74: FDA recently issued the guidance *PET Drugs – Current Good Manufacturing Practice (CGMP) (Small Entity Compliance Guide)* that appears to be identical to the guidance issued in December 2009. Is there a definition of small entity? Does the August 2011 version differ from the version dated December 2009?

There are no substantive differences between the Small Entity Compliance Guide and the guidance published in December 2009. The Small Entity Compliance Guide on Drug CGMPs was prepared to comply with section 212 of the Small Business Regulatory Enforcement Fairness Act (Public Law 104-121). The Act states the following:

> For each rule or group of related rules for which an agency is required to prepare a final regulatory flexibility analysis under section 605(b) of title 5, United States Code, the agency shall publish 1 or more guides to assist small entities in complying with the rule and shall entitle such publications "small entity compliance guides."

A definition for *small entity* can be found in section 211 of the Act.

Q75: Is identity testing on mannose triflate required? If required, does it need to be a specific identity test?

Although an identity test on incoming components is required to be performed, a specific identity test is not needed under certain conditions (see 21 CFR 212.40(c). When the finished-product testing of a PET drug product includes testing to ensure that the correct components have been used, the PET drug producer need only determine that each lot of incoming components complies with written specifications by examining a certificate of analysis provided by the supplier (21 CFR 212.40(c)(1)(i)). We believe that the use of this type of finished-product testing makes specific identity testing of components redundant and unnecessary. For example, when identity of the F18 radionuclide is established as part of the finished-product testing and the method of production used is well-documented and understood, it can be reasonably argued that the component that yields this radionuclide is likely to be O 18 water. In this case, a specific identity test for O 18 water is not necessary before the lot is used in production. Similarly, a specific identity test before using a lot of mannose triflate might be redundant and unnecessary when (1) a well-understood method of synthesis of FDG is used, (2) a test to confirm the radiochemical identity is performed in the finished drug product, and (3) the mannose triflate was obtained from a reliable supplier with whom a relationship has been previously established and is accompanied by a certificate of analysis.

Q76: What is FDA's current thinking on conditional final release testing if there was a problem or malfunction?

Under the CGMP regulations at 21 CFR 212.70, you may not release another batch of the PET product until you have corrected the problem concerning the malfunction of analytical equipment. A reserve sample is needed to complete the finished product testing.

Q77: Which analytical techniques, if any, require validation?

New analytical procedures must be validated appropriately based on the intended use (see 21 CFR 212.60(c)). A compendial method, generally, does not need to be validated. However, you will need to show that the method is suitable for your product, analytical equipment, and system used. The following guidances may be useful in determining which parameters to validate:

- *Text on Validation of Analytical Procedures* (ICH Q2A)
- *Q2B Validation of Analytical Procedures: Methodology*
- *Analytical Procedures and Methods Validation*[6]
- *Validation of Chromatographic Methods*

Q78: Although the radiosynthesis is processed in the hot cell, some operations are performed in the laboratory, such as HPLC operation, buffer preparation, and weighing raw materials on a scale. Is there any specified quality for the ceiling and floor (e.g., should we use seamless, washable material)?

No. The ceiling, floor, and walls of the production and laboratory work area for PET drugs must be clean and designed to minimize the level of particulate contamination in the processing area of the final product (see 21 CFR 212.30). However, if you are constructing a new PET facility, seamless ceilings and floors are recommended to help ensure that they can be readily and thoroughly cleaned.

Q79: Can the PET drug solution obtained from a synthesizer in the final product vial assembly be diluted to make the final formulation solution outside of the controlled environment?

USP chapter <823> states that "solutions for parenteral administrations must be filter sterilized and aseptically transferred to a sterile, nonpyrogenic" vial. Further, the chapter also stipulates that aseptic manipulations must be performed within the aseptic hood. The final product vial assembly (everything that is post sterile filter and including the sterile

[6] This draft guidance, when finalized, will represent FDA's current thinking on this topic.

filter) should be assembled in an aseptic hood using aseptic techniques. All entries into the sterile final product vial should be done using aseptic techniques. To mitigate the risk of contamination, we recommend that the direct dilution of the product be performed in the laminar flow hood. See also 21 CFR 212.30 and the guidance *Media Fills for Validation for Aseptic Preparations for PET Drugs*.

Q80: Is it acceptable for the laminar flow hood to be in the same workspace as the production?

Yes, it is acceptable to have the laminar flow hood in the same workspace. Controls should be in place to prevent mix-ups and the potential for contamination. FDA expects that the hood would be placed in a controlled and clean area.

Q81: At some sites, the drug product is synthesized and transferred into a dispensing cell in the Radiopharmacy, at which time the Quality Control (QC) sample, sterility sample, and retention sample are extracted just before drawing the finished unit dose for administration. How would FDA like to see the segregation of manufacturing activities from pharmacy practice activities?

Although there is no specific FDA requirement that manufacturing and pharmacy activities should be in separate areas, pharmacy activities and relevant facility control should comply with State Pharmacy regulation and USP chapter <797>.

If the proposed product is a multidose vial or a pharmacy bulk package, the operations leading up to the production of these containers are considered to be manufacturing operations. In this case, the QC sample must be obtained from the multidose vial with appropriate sampling if multiple containers are manufactured in a batch. If the "HOW SUPPLIED" section of the labeling indicates that the drug is supplied as a multidose container or as a pharmacy bulk pack and the multidose vial or the pharmacy bulk pack is released to the pharmacy, dispensing into unit doses (under the practice of pharmacy) is considered a pharmacy operation.

Q82: Can the PET radiopharmaceutical manufacturing activities be conducted in the same room as the PET dose dispensing?

Yes, the production of PET drug products and the dispensing by prescription of patient-specific doses of PET drug in the practice of pharmacy may be done in the same work area. The area of the facility for these two activities and the work flow should be designed to prevent contamination and mix-ups.

Q83: Can the QC samples be drawn from the vial in the same hot cell where the PET doses are dispensed?

It is acceptable for the drawing of QC samples from a PET drug product batch vial in the hot cell provided there are proper controls in place to prevent contamination and ingress into the product vial. It is, however, preferable to withdraw the QC sample in the laminar flow workstation to mitigate risk of microbial and particulate contamination. This is the case when the dilution to the bulk sample vial is conducted in the laminar flow workstation where the dose calibrator is located.

Q84: What is the proper procedure for dispensing the pharmacy dose?

The dispensing of the pharmacy dose should not be done inside the hot cell. Pharmacy dispensing into individual prescription dose should be done under laminar flow, complying with State Pharmacy regulation and USP chapter <797>.

Q85: Please clarify the environmental air quality expectations and/or requirements for different areas within a PET manufacturing site. In general, what are the minimal environmental air quality monitoring requirements?

The air quality in the production and laboratory areas should be controlled to minimize the level of contamination (particulate and microbial) that may affect analyses or the quality, purity, and strength of the PET drug.

The air quality in the hot cell should be clean and controlled to minimize the level of particle and microbial contaminants that may affect the quality of the PET drug. We recommend the use of High-Efficiency Particulate Air (HEPA) filtered air for this environment when the product is being sampled or diluted to reduce the possibility of microbial contamination.

Aseptic workstations (hoods) should meet Class 100 conditions using HEPA filtered laminar flow air. We recommend that these workstations be located in the facility away from foot traffic and other activity to reduce the chance of disruption to air flow and contamination of the workstation.

Q86: Is it acceptable to use settling plates for environmental monitoring or will there be a requirement to use an active air sampling system?

Yes, settling plates are acceptable. We recommend that microbial monitoring of the aseptic workstation be conducted during sterility testing and critical aseptic manipulations. The methods used may also include active air sampling.

Q87: Inspections have raised issues over the requirement of mandatory standards for cyclotron maintenance, including target rebuilds. Can FDA comment on the

relevance of the request given the nature of the performance of the cyclotron and final product testing?

FDA has not imposed any mandatory standards for cyclotron maintenance or target rebuild. Some attention may be devoted during an inspection to target window maintenance because over a period of time, the target window foils may get etched by the target beam that may cause leaching of unintended material (including radionuclides) into the irradiated isotopic solution.

Inspectors may review the records on target window maintenance (including target window rebuild) to identify any problems encountered, and corrective actions. Usually, inspectors will only devote attention to this issue if a quality problem has been identified.

Q88: Are we required to submit a Field Alert Report to FDA on the failure of a distributed batch to meet the specifications (e.g., sterility) established in the application?

Yes (see 21 CFR 314.81). This also applies to PET drugs with an application pending FDA approval.

Q89: If a PET producer submits a supplement to add a manufacturing facility or facilities, how much media fill data should be submitted in the supplement?

If the new facility (or facilities) uses the same media fill methods and criteria that were approved in the application, the supplement should refer to the approved application and provide brief summaries of the media fill process descriptions and acceptance criteria for all sites, along with a statement indicating that the media fills met their acceptance criteria. The raw data should be available on site for examination during an FDA inspection.

If the additional facility (or facilities) uses different manufacturing processes or media fill procedures, the new media fill procedures and acceptance criteria would need to be described in the supplement and reports for each facility's aseptic process validation should also be submitted.

D. Inspections

Q90: The FD&C Act specifies that drug producers will be inspected once every 2 years. FDA previously stated that FDA will continue to perform surveillance inspections of a number of PET facilities each year. Please clarify the expected inspection profile.

We expect to perform a CGMP surveillance inspection of each PET facility once every 2 years on average, but may visit some sites more than once every 2 years when warranted, such as when the site is named in an application for a new type of PET product or has undergone substantial change.

Q91: Will PET facilities submitting applications and registering in accordance with section 510 of the FD&C Act (21 U.S.C. 360) be inspected before approval of their ANDA and/or NDA? If so, under what time frame and against what inspection criteria?

As part of the drug approval process, a preapproval inspection (PAI) will be performed to provide assurance that a PET drug production facility that is named in a drug application is capable of producing the PET drug in accordance with CGMPs, and that the submitted application data are reliable, accurate, and complete. FDA intends to prioritize inspections to ensure facilities referenced in applications are inspected before the application is ready for approval. Your facility should be ready for inspection when the application is submitted.

The inspection criteria are described in Compliance Program 7356.002P (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM277416.pdf).

Q92: Is a large-enough, dedicated cadre of trained inspectors available to ensure complete review of manufacturing sites in timely fashion?

FDA has trained a cadre of inspectors, and we expect that inspections will be conducted in a timely manner.

Q93: For applications with multiple manufacturing sites, will FDA use a risk-based approach to select sites for inspection?

No. At the beginning of our PET facility inspection program, it would be difficult to assess the risks at particular sites given that most facilities have never been inspected. After we gain sufficient experience with PET facilities, we may consider changing to a more risk-based approach.

Q94: During inspections, will FDA take into consideration that some SOPs might be based on USP chapter <823> while others might be based on 21 CFR part 212, as producers transition from compliance with the USP to the part 212 regulations?

Yes, FDA will take the transition into consideration during inspections.

Q95: Can the initial FDA inspection for an academic setting be scheduled in advance since academic sites do not have a corporate quality assurance office to guide the investigator through the facility and associated paperwork?

Yes, it can be scheduled in advance. However, for-cause inspections are usually not preannounced. It is important for a site to have records and information properly organized to facilitate an efficient inspection (see 21 CFR 212.110).

Q96: For companies that have multiple production facilities, is there a way to address the corrections at multiple sites as we are developing our responses to the Form 483 (i.e., the list of objectionable observations)?

If at the corporate level you are aware of sites having problems, you should initiate that discussion with CDER's Office of Manufacturing and Product Quality, Division of Domestic Drug Quality. CDER will involve the districts where your manufacturing sites are located in the review of your response and correction of the problems. Companies with multiple sites should consider whether objectionable findings at any one site are also applicable to other sites, and make necessary corrections at all affected sites whether or not FDA has inspected and found similar problems.

E. Registration and Listing

Q97: How does drug registration relate to ANDAs, NDAs, and standard product labeling (SPL)?

Manufacturers are required to register all facilities where they produce PET drugs and list all PET drugs that are made at each facility (see 21 CFR part 207). Further information is available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/ucm078801.htm.

Q98: Is it appropriate to register as a manufacturing site ahead of submitting our ANDA?

Yes, you should register as soon as possible if you are already making PET drugs, and you may register ahead of submitting your ANDA if you are not currently making PET drugs. Please note that 21 CFR 207.21 requires registration within 5 days after first manufacturing batches for distribution or submission of an NDA or ANDA.

F. User Fees

Q99: Considering the March 10, 2000, PET Safety and Effectiveness Notice (65 FR 12999), what fees associated with an NDA for FDG, Ammonia N13, or Sodium Fluoride F18 may be waived?

If you submit your NDA in accordance with the March 10, 2000, PET Safety and Effectiveness Notice, your application fee will be waived. You will still be assessed the product and establishment fees. However, you can request a waiver of the product and establishment fees under the public health or barrier-to-innovation waiver. See responses to questions posed on December 9, 2009, at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm193476.htm.

Q100: Will FDA waive application fees for other PET NDAs like it did for FDG, Ammonia N13, and Sodium Fluoride F18?

FDA does not intend to provide a blanket waiver of application fees for NDAs for other PET drugs. We will consider requests for waivers of fees on a case-by-base basis. We recommend that you submit any request for a fee waiver sufficiently in advance of submitting your application so that we have sufficient time to process it and provide a response before you submit your application. There is no time limit for FDA to process a waiver request, but we attempt to process requests for waivers of application fees within 90 days of receipt of the request.

Q101: When a product that is the same as an innovator product is approved and marketed under an ANDA, the innovator product is no longer assessed annual product and establishment fees. Does this only apply to the RLD when an ANDA for the same strength is approved and marketed or do all NDAs for that product get an exemption?

The ANDA product must be the same strength as the RLD for the RLD to get the benefit of an exemption. See our responses to Q32 and Q43 for additional information on determining the strength of PET products.

Q102: If an applicant identifies several different categories of waivers and exemptions for which it might qualify, is it best to list all of them in the request or should only one be chosen?

We encourage persons requesting a waiver to identify all the waivers and exemptions for which they may qualify.

Q103: Do ANDA applicants need to obtain a waiver of fees before they submit their application?

No. PET drug ANDAs (both applicants and facilities) are exempt from generic drug user fees. Applicants do not need to request any waivers or exemptions before submitting their applications.

Q104: Would a nonprofit university that is affiliated with and distributes PET drugs to a veterans hospital be exempt from fees under the State and Federal government exemption?

If the State or Federal government-affiliated university distributes its product commercially, meaning any distribution for financial reimbursement, goods, or services, whether or not the amount of the charge covers the full costs associated with the product, then the State or Federal government exemption would not apply (see the guidance *User Fee Waivers, Reductions, and Refunds for Drug and Biological Products).* It would not matter that the university distributed to the veterans hospital. The key point is whether the product is distributed commercially. However, if the State or Federal government-affiliated university gives the product away without any reimbursement, then the State or Federal government exemption would apply. Please note that any recovery by a university of all or parts of the costs of the manufacture or distribution of a product makes the distribution commercial.

APPENDIX A – PET NDA AND ANDA REGULATORY SCENARIOS

Your Facility's Status	You Submitted an NDA or ANDA for the Particular Drug Before 6/12/2012	You Did Not Submit an NDA or ANDA for the Particular Drug Before 6/12/2012	You Submitted an IND for the Particular Drug Before or After 6/12/2012
Your facility was producing Fludeoxyglucose F18 injection (FDG), Ammonia N13 injection (Ammonia), or Sodium Fluoride F18 injection (NaF), for clinical use* before 6/12/2012 (note that each drug is to be considered independently).	FDA intends to exercise enforcement discretion and you can continue making the PET drug for clinical use while the NDA or ANDA review is pending. *** If the Office of New Drugs (OND) issues a Refuse to File letter or OGD issues a Refuse to Receive letter based upon inadequacy of the submitted documents, you must halt production.	If you continue to produce FDG, NaF, or Ammonia for clinical use after 6/12/2012, you may be subject to enforcement action until you submit an NDA or ANDA. Once your application is submitted and has been filed, you may resume production while review is pending. *** If OND issues a Refuse to File letter or OGD issues a Refuse to Receive letter based upon inadequacy of the submitted documents, you must halt production.	You may not continue to produce FDG, NaF, or Ammonia for clinical use under an IND. You must have submitted an NDA or ANDA or you may be subject to enforcement action. You must submit an IND if you are developing FDG, NaF, or Ammonia for a new use for which you intend to submit an NDA, and the other criteria for when an IND is required are met.
Your facility was not producing FDG, NaF, or Ammonia for clinical use before 6/12/2012, but you would like to start production for clinical use.*	FDA intends to exercise enforcement discretion and you may begin production for clinical use while the review of your NDA or ANDA is pending. *** If OND issues a Refuse to File letter or OGD issues a Refuse to Receive letter based upon inadequacy of the submitted documents, you must halt production.	You may not begin production of FDG, NaF, or Ammonia for clinical use until you have an approved NDA or ANDA. If you begin production without an approved NDA or ANDA, you may be subject to enforcement action.	You may not begin to produce FDG, NaF, or Ammonia for clinical use under an IND. You must have submitted an NDA or ANDA or you may be subject to enforcement action. You must submit an IND if you are developing FDG, NaF, or Ammonia for a new use for which you intend to submit an NDA, and the other criteria for when an IND is required are met. You may begin production of the drug for this *investigational use***** under a traditional IND 30 days after FDA receives the IND unless the investigation is put on clinical hold.

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Appendix A (continued)

Your Facility's Status	You Submitted an NDA or ANDA* for the Particular Drug Before 6/12/2012	You Did Not Submit an NDA or ANDA for the Particular Drug Before 6/12/2012	You Submitted an IND for the Particular Drug Before or After 6/12/2012
Your facility was producing PET drugs other than FDG, NaF, or Ammonia for clinical use* before 6/12/2012 (e.g., Fluorodopa F18 injection, Choline C-11 injection).	If you submitted an NDA for that particular drug, ** you may continue production while the NDA is under review. *** If the Office of New Drugs issues a Refuse to File letter based upon inadequacy of the submitted documents, you must halt production.	If the PET drug would be difficult to commercialize because of the unique circumstances of its production (e.g., the isotope properties, very short half-life) and nature of use (e.g., use is limited to a small niche population), you may produce the PET drug for clinical use under an expanded access IND if the criteria are met. See guidance *Investigational New Drug Applications for Positron Emission Typography (PET) Drugs*. If you continue to produce the drug for clinical use without submitting an NDA or an expanded access submission, you could be subject to enforcement action until an NDA or IND is submitted. Once an NDA** is submitted or the IND is allowed to proceed, you could resume production while review of the NDA is pending*** or as long as the IND remains in effect.	FDA intends to exercise enforcement discretion and you may continue production of the drug for clinical use while your expanded access IND is under review unless the IND is put on clinical hold.
Your facility was not producing PET drugs other than FDG, NaF, or Ammonia for clinical use before 6/12/2012, but you would like to start production of a new PET drug for clinical use.*	You may not begin production for clinical use until you have an approved NDA** unless you have an expanded access IND in effect.	You may not begin production for clinical use until you have an approved NDA, ** unless you have an expanded access IND in effect. If the PET drug would be very difficult to commercialize because of the unique circumstances of its production (e.g., the isotope properties, very short half-life) and nature of use (e.g., use is limited to a small niche population), you may produce the PET drug for clinical use under an expanded access IND if the criteria are met. See guidance *Investigational New Drug Applications for Positron Emission Typography (PET) Drugs*.	You may begin production of the drug for clinical use under an expanded access or traditional IND 30 days after IND submission unless the IND is put on clinical hold.

**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.
**At this time, ANDAs may not be submitted for PET drugs other than FDG, Ammonia N13, and Sodium Fluoride F18.

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Appendix A (continued)

***If problems are detected during an inspection, FDA may require you to stop production. You will be expected to have an approved application by December 12, 2015, or halt production.

****Investigational use, as distinguished from clinical use, is use in a study of the drug to establish the safety and/or efficacy of a new use of the drug to support an application for approval of that use. Investigational use may also refer to use of certain PET drugs for clinical purposes under an expanded access IND.

APPENDIX B – CHANGES IN EQUIPMENT OR FACILITIES
(APPLIES ONLY TO FDG, AMMONIA, AND N**a**F)

Your Status	The Equipment and Procedures Are Identical	The Equipment Is Different, But Does Not Result in Any Formulation or Strength Change	The Equipment and Procedures Are Different, Resulting in a Formulation or Strength Change
You submitted an NDA or ANDA before 6/12/2012, and you want to add or replace production equipment described in the application at the facility described in the application before the NDA or ANDA is approved.	You do not need to amend the application. You can make this change under your quality systems. The change validation data will be subject to audit during the PAI inspection. See the ICH guidance for industry *Q10 Pharmaceutical Quality System*.	You must amend the application to describe the new equipment and procedures and provide supporting data for the change. If you submit an appropriate amendment to the pending application to add the equipment, you may begin production for clinical use while the NDA or ANDA review is pending. *	You cannot change formulation or strength in an ANDA, although you may change exception excipients (buffers, preservatives, or antioxidants). Any other change in formulation from the reference listed drug (RLD) requires an NDA or a separate ANDA that references another designated RLD. ** Any change in strength from the RLD requires an NDA or a suitability petition and a new ANDA. If the exception excipients change, you must amend the application to describe the new equipment and procedures and the change to the exception excipients, and provide supporting data for the change. If you submit an appropriate amendment to the pending application to add the equipment, you may begin production for clinical use while the NDA or ANDA review is pending.*
You submitted an NDA or ANDA before 6/12/2012, and you want to add additional production facilities to your application before the application is approved.	You must amend the application to describe the new facility and provide new CMC data for the drug produced at the new facility. See the ICH guidance for industry *Q10 Pharmaceutical Quality System*. If you submit an appropriate amendment to the pending application to add the equipment or production facility, FDA intends to exercise enforcement discretion and you may begin production for clinical use while the NDA or ANDA review is pending. *	You must amend the application to describe the new facility and provide new CMC data for the drug produced at the new facility. If you submit an appropriate amendment to the pending application to add the equipment or production facility, you may begin production for clinical use while the NDA review is pending. *	You cannot change formulation or strength in an ANDA, except you may change exception excipients (buffers, preservative, or antioxidants). Any other change in formulation from the reference listed drug (RLD) requires an NDA. Any change in strength from the RLD requires an NDA or a suitability petition and a new ANDA. **

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Appendix B (continued)

Your Status	The Equipment and Procedures Are Identical	The Equipment Is Different, But Does Not Result in Any Formulation or Strength Change	The Equipment and Procedures Are Different, Resulting in a Formulation or Strength Change
Your facility is producing a PET drug under an approved NDA or ANDA, and you want to add or replace production equipment described in the application at the facility described in the application.	No supplement is required. You can make this change under your quality systems. The change validation data will be subject to audit during the surveillance inspection. We suggest that you provide this information in your annual report.	You must submit a supplement to the application under 21 CFR 314.70 that describes the new equipment and provides data supporting the change. You may not begin production for clinical use using the new equipment until the NDA or ANDA supplement is approved or accepted as a changes being effected (CBE) supplement under 21 CFR 314.70.	You must submit a supplement to the application under 21 CFR 314.70 that describes the new equipment and provides data supporting the change. You may not begin production for clinical use using the new equipment until the NDA or ANDA supplement is approved or accepted as a CBE supplement under 21 CFR 314.70.*
Your facility is producing a PET drug under an approved NDA or ANDA, and you want to add an additional production facility.	You must submit a supplement to the application to describe the additional production facility and provide new CMC data for the drug produced at the new facility. You may not begin production at the new facility until the supplement is approved or accepted as a CBE supplement under 21 CFR 314.70.	You must submit a supplement to the application under 21 CFR 314.70 to describe the additional production facility and provide new CMC data for the drug produced at the new facility. You may not begin production at the new facility until the supplement is approved or accepted as a CBE supplement under 21 CFR 314.70.	You must submit a supplement to the application under 21 CFR 314.70 to describe the new production facility and provide new CMC data for the drug produced at the new facility. You may not begin production at the new facility until the supplement is approved or accepted as a CBE supplement under 21 CFR 314.70.

*If problems are detected during an inspection, you might need to stop production. Production of a PET drug not under an approved NDA or ANDA while an NDA or ANDA review is pending is only allowed through December 12, 2015.
**FDA may designate more than one PET drug product as an RLD if the formulations of the approved products are different with respect to non-exception excipients (e.g., tonicity agent) and the differences in formulation would require an ANDA applicant to cite a different RLD.