Guidance

PET Drug Applications — Content and Format for NDAs and ANDAs

- **Fludeoxyglucose F 18 Injection**
- **Ammonia N 13 Injection**
- **Sodium Fluoride F 18 Injection**

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2011
Procedural

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Contains Nonbinding Recommendations

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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

On December 9, 2009, FDA issued a final current good manufacturing practice (CGMP) regulation for the production of positron emission tomography (PET) drugs.[2] Under the requirements of section 121 of the Food and Drug Administration Modernization Act (FDAMA), within two years following this publication date, an NDA or ANDA must be submitted for any PET drug marketed for clinical use in the United States.

This guidance is intended to assist applicants in preparing new drug applications (NDAs) or abbreviated new drug applications (ANDAs) for fludeoxyglucose F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection used in PET imaging for the indications cited in Section III (below). FDA approval of an NDA or ANDA will make it possible to market these PET drugs for clinical use according to the requirements of the Federal Food, Drug, and Cosmetic Act (the Act).[3]

The guidance (1) provides brief background information, (2) makes recommendations to help you decide whether you should submit an NDA or an ANDA, (3) includes a description of the content and format needed in an NDA and an ANDA, and (4) provides boxed text that you can copy or cut and paste into your application. The content and format sections provide information

[1] This guidance has been prepared by the PET Steering Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] The regulation, CGMP guidance, and supportive information, including historical documents are available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm.

[3] NDAs, including 505(b)(2) applications, are submitted under section 505(b) of the Act. Section 505(j) of the Act applies to ANDAs.

required to submit an NDA or an ANDA for these PET drugs. Finally, we have developed sample formats for the chemistry sections and for the proposed labeling for fludeoxyglucose F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection as well as 356h sample forms. These formats are supplied as separate documents on FDA's web site.[4]

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 apply. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Because this guidance discusses in great detail what *must be* submitted in an NDA (particularly a 505(b)(2) NDA) or an ANDA (505(j)), the guidance differs from most guidances in that it contains extensive mandatory language, especially in the Appendices. This mandatory language is used whenever the Act and/or FDA regulations require the submission of certain information. Unlike other documents in which mandatory language is accompanied by the related cite, to make the guidance more user friendly and less cumbersome, we do not cite each regulation each time we discuss a requirement.

II. BACKGROUND

On November 21, 1997, President Clinton signed FDAMA into law (Pub. L. 105-115). Section 121(c) of the Modernization Act directed FDA to regulate PET drugs. Section 121 identified a number of tasks for the FDA including:

- Develop appropriate procedures for the approval of PET drugs as well as CGMP requirements for such drugs.

- Consult with patient advocacy groups, professional associations, manufacturers, and persons licensed to make or use PET drugs in the process of establishing these procedures and requirements.

- Do not require the submission of NDAs or ANDAs for compounded PET drugs that are not adulterated as described in the Act for a period of four years after the date of enactment or 2 years after the date FDA adopts special approval procedures and CGMP requirements for PET drugs, whichever is longer. Nothing prohibits the voluntary submission and FDA review of such applications.

Beginning in 1997, FDA took a series of actions, which are summarized here.

- The Agency conducted several public meetings with various representatives of an industry trade association, the Academy for Molecular Imaging (formerly the Institute for

[4] See http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065015.htm and http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm241316.htm.

Clinical PET (ICP)), and other interested persons to discuss FDA proposals for PET drug approval procedures and CGMP requirements.

- Because certain PET drugs have been used clinically for a number of years, FDA conducted its own review of the published literature[5] to evaluate the safety and effectiveness of the PET drugs in widespread use for certain indications to facilitate the process of submitting applications for these products.
- The Agency discussed its preliminary findings on the safety and effectiveness of fludeoxyglucose F 18 injection (for the assessment of malignancy as well as left ventricular myocardial viability) and ammonia N 13 injection (for assessing myocardial perfusion) with the ICP and other interested persons at public meetings on November 17, 1998, and February 18-19, 1999.
- On June 28-29, 1999, the Agency presented its findings to its Medical Imaging Drugs Advisory Committee (Advisory Committee). The Advisory Committee concluded that fludeoxyglucose F 18 injection and ammonia N 13 injection can be considered safe and effective for these indications, although it recommended some revisions to the wording of the indications proposed by FDA.
- In a notice in the *Federal Register* in March 2000 (the PET Safety and Effectiveness Notice),[6] FDA presented its findings of safety and effectiveness for the PET drugs studied for certain indications and described the types of applications that can be submitted for fludeoxyglucose F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection used in PET imaging (see Section III). These findings fulfill the requirement to develop appropriate approval procedures for these PET drugs.
- In April 2002, FDA issued a preliminary draft proposed CGMP regulation and a draft guidance on CGMP requirements for public comment; a proposed rule and revised draft guidance were issued in September 2005, to solicit additional public input.
- In December 2009, after carefully considering all public input, FDA published a final CGMP regulation, triggering the two-year time period for applicants to submit an NDA or ANDA for any PET drug used clinically.

PET drug application submissions must be received by the agency on or before December 12, 2011. FDA will not grant an extension for submitting applications. However, applicants may continue to use a PET drug while their NDA or ANDA is under review. FDA intends to exercise enforcement discretion regarding unapproved PET drugs while submissions are reviewed. However, FDA expects that by December 12, 2015, all PET drugs in commercial clinical use (i.e., not used under RDRC or IND) will be used under approved applications and does not intend to exercise enforcement discretion beyond that date.

[5]As stated in FDA guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*, FDA may, in certain circumstances, rely on published literature alone to support the approval of a new drug product under section 505 of the Act.

[6] 65 FR 12999, March 10, 2000.

III. SUMMARY OF PET POLICY

Based on the findings elucidated in the March 2000 PET Safety and Effectiveness Notice, FDA has determined that you are not required to conduct clinical trials or submit new safety and effectiveness information to obtain approval for fludeoxyglucose F 18 injection, ammonia N 13 injection, or sodium fluoride F 18 injection used in PET imaging. You need only reference in your marketing application the published literature and/or FDA's determination of safety and effectiveness for these drugs described in the PET Safety and Effectiveness Notice provided that you are seeking approval of the following indication(s):

Fludeoxyglucose F 18 Injection

1. Fludeoxyglucose F 18 Injection is indicated in PET imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.

2. Fludeoxyglucose F 18 Injection is indicated in PET imaging in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.

3. Fludeoxyglucose F 18 Injection is indicated in PET imaging in patients for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

Ammonia N 13 Injection

4. Ammonia N 13 Injection is indicated for diagnostic PET imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease.

Sodium Fluoride F 18 Injection

5. Sodium fluoride F 18 Injection is indicated for diagnostic positron emission tomography (PET) imaging of bone to define areas of altered osteogenic activity.

IV. SHOULD I SUBMIT AN NDA OR AN ANDA?

An applicant seeking approval for fludeoxyglucose F 18 injection, ammonia N 13 injection, or sodium fluoride F 18 injection may submit an NDA or an ANDA, depending whether or not the specific drug product is the same as an already approved drug formulation and the indications for which approval is sought.

A. Submitting an NDA for a PET Drug

Generally, you would submit an NDA if your product is not the same as an already approved product. An NDA for the PET drugs discussed in this guidance is of the type described in section 505(b)(2) of the Act, which generally relies for approval on (1) references to studies conducted by others and for which the applicant does not have a right of reference and/or (2) findings of safety and effectiveness for previously approved products and/or (3) published literature. An applicant submitting a 505(b)(2) NDA for a PET drug can rely on FDA's review of the literature as described in the PET Safety and Effectiveness Notice and/or on FDA's findings with respect to previous approvals of PET drugs for certain indications.[7]

B. Submitting an ANDA

1. Generally

An ANDA is usually submitted for a drug product that is ***the same as*** an already approved drug (a listed drug).[8] When an applicant submits an ANDA based on a listed drug, the previously approved drug product on which the ANDA relies is officially known as the *reference listed drug* (RLD).[9] The proposed drug product for which approval is sought in an ANDA submitted under section 505(j) of the Act is commonly referred to as a *generic drug*.

FDA regulations (21 CFR 314.92(a)(1)) 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* (with certain exceptions) *conditions of use* as its RLD.[10] Differences in the manufacturing processes do not affect whether a product may be approved under an ANDA. The strength is compared based on stated strength at the time of calibration, which for a multi dose vial of a PET drug is generally at the end of synthesis (EOS). EOS is taken to mean at the end of manufacturing of the finished drug product. For unit dose vials, the strength is calibrated to a particular time from the end of synthesis of a unit dose (for example see NDA 17-042). Such drugs must also be bioequivalent to that RLD.[11] Because there are already approved NDAs for fludeoxyglucose F 18 injection, sodium fluoride F 18 injection, and ammonia N 13 injection for specific indications, you could submit an ANDA — ***if your product is the same as the approved product and you are seeking approval only for the already approved indications.***

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[7] The PET Safety and Effectiveness Notice includes a detailed description of 505(b)(2) NDAs.

[8] A *listed drug* is defined as a new drug product that has an effective approval under section 505(c) of the Act for safety and effectiveness or under section 505(j) of the Act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the Act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness (21 CFR 314.3(b)).

[9] A *reference listed drug* is defined as the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application (21 CFR 314.3(b)). FDA lists approved drugs that may be referenced in an ANDA in the *Approved Drug Products With Therapeutic Equivalence Evaluations* (the *Orange Book).* The *Orange Book* is updated by a monthly cumulative supplement.

[10] It should be noted that the comparison is between the generic and RLD finished products.

[11] 21 CFR 314.94 and 314.127.

Although drugs approved in ANDAs are generally the same as the RLD, there are differences that may be permitted. If your proposed (test) drug differs from the RLD in certain ways, as discussed below, you can still submit an ANDA. In some cases, though, you must first submit and obtain approval of a *suitability petition* under 21 CFR 314.93. This process could lengthen the time it takes for your application to be approved.

Before beginning to fulfill the submission requirements for the ANDA, you should determine whether your product is the same as the listed drug you reference (RLD). The following tables describe approved PET products. Generally, your product should be the same as one of the RLDs. (There are multiple RLDs for fludeoxyglucose F18 injection as well as an approved suitability petition[12]). Certain differences between the generic drug and the RLD are permitted. Such differences are addressed below.[13]

Fludeoxyglucose F 18 Injection (NDA 20-306)

Active ingredient	2-Deoxy-2[^{18}F]fluoro-D-glucose
Inactive ingredients	Sodium chloride injection, USP (9 mg/mL sodium chloride in water for injection (WFI))
Dosage form	Injection
Specific activity	No-carrier added
Strength (radioconcentration)	4 - 90 mCi/mL at EOS (end of synthesis)
Osmolality	Isotonic
pH	5.5 - 7.5
Route of administration	Intravenous

Fludeoxyglucose F 18 Injection (NDA 21-768)

Active ingredient	2-Deoxy-2[^{18}F]fluoro-D-glucose
Inactive ingredients	Sodium chloride (4.5 mg/mL), Citrate (7.2 mg/mL) in water for injection (WFI)
Dosage form	Injection
Specific activity	No-carrier added
Strength (radioconcentration)	10-100 mCi/mL at EOS (end of synthesis)
Osmolality	Isotonic
pH	5.0 – 7.5
Route of administration	Intravenous

Fludeoxyglucose F 18 Injection (NDA 21-870)

Active ingredient	2-Deoxy-2[^{18}F]fluoro-D-glucose
Inactive ingredients	Sodium chloride (4.5 mg/mL), Citrate (7.2 mg/mL) in water for injection (WFI)
Dosage form	Injection
Specific activity	No-carrier added
Strength (radioconcentration)	20-300 mCi/mL at EOS (end of synthesis)
Osmolality	Isotonic
pH	5.5 - 7.5
Route of administration	Intravenous

[12]There is an approved ANDA suitability petition for fludeoxyglucose F 18 injection that involves changes in strength, including mCi/mL, and total activity from the RLD (Docket No. FDA 2010-P-0444).

[13] The information used to formulate these tables is presented in the Orange Book and the product labeling available at http://dailymed.nlm.nih.gov/dailymed.

Sodium Fluoride F 18 Injection (NDA 17-042)

Active ingredient	Sodium fluoride F 18
Inactive ingredients	Sodium chloride injection, USP (9 mg / mL sodium chloride in water for injection (WFI))
Dosage form	Injection
Specific activity	No-carrier added
Strength (radioconcentration)	2 mCi/mL at calibration
Osmolality	Isotonic
pH	6 – 8
Route of administration	Intravenous

Sodium Fluoride F 18 Injection (NDA 22-494)

Active ingredient	Sodium fluoride F 18
Inactive ingredients	Aqueous 0.9% sodium chloride
Dosage form	Injection
Specific activity	No-carrier added
Strength (radioconcentration)	10 - 200 mCi/mL at EOS (end of synthesis)
Osmolality	Isotonic
pH	4.5 – 8.0
Route of administration	Intravenous

Ammonia N 13 Injection (NDA 22-119)

Active ingredient	Ammonia N 13
Inactive ingredients	0.9% aqueous sodium chloride
Dosage form	Injection
Specific activity	10-20 mCi dose contains 8.47-16.94 picograms (theoretical calculated) of ammonia. No-carrier added.
Strength (radioconcentration)	3.75-37.5 mCi/mL (30 mCi-300 mCi/8 mL) at EOS (end of synthesis)
Osmolality	Isotonic
pH	4.5 - 7.0
Route of administration	Intravenous

2. In What Ways May a Generic PET Drug Differ from the RLD?

Generally, 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 also bioequivalence determination criteria in section V.C. below).[14] Additional differences in non-exception excipients are generally not permitted.

See Appendix B for a more detailed description of permissible differences between a generic PET drug and the RLD.

[14] See 21 CFR 314.94(a)(9)(ii) and (iii).

3. What is a Suitability Petition?

If your drug differs from the RLD in *strength, route of administration*, or *dosage form*, you can still submit an ANDA, but you must first submit a suitability petition to obtain permission to file an ANDA with such a change (21 CFR 314.93). For example, a change in the specific concentration (in mCi/mL), and/or in the amount of active ingredient is considered a change of strength and may be permitted in an ANDA with approval of a suitability petition. The suitability petition must be approved before the ANDA is filed. As noted above, this process could lengthen the time it takes for your application to be approved.

You will have to demonstrate in the suitability petition that, among other things, clinical investigations will not be required to establish the safety or effectiveness of the petitioned product. If your proposed version of one of the PET RLDs listed above differs from the RLD in dosage form, strength, or route of administration, and you decide that you do not wish to submit an ANDA suitability petition, you still have the option of submitting a 505(b)(2) NDA.

After an ANDA suitability petition is approved for a change to a product, any applicant (not just the applicant who submitted the suitability petition) may refer to that petition as the basis for submission of an ANDA. When the ANDA is submitted, you should refer in your ANDA to the appropriate petition docket number and include a copy of the letter approving the suitability petition in the ANDA submission. Section IV.B.1., describing approved PET drug products, notes applicable approved suitability petitions that may be referred to in an ANDA.[15] Once an application is approved for a product that is the same as the subject of an approved suitability petition, that drug product will be a listed drug. Thereafter, generally, you should refer to that listed drug and not to the petition as the basis for submission of an ANDA.

If you have any questions about submitting an ANDA or about suitability petitions, please contact the Office of Generic Drugs.

C. General Recommendations

FDA recommends the following application types for each of the three PET drugs discussed in this guidance.[16]

1. Fludeoxyglucose F 18 injection

Three NDAs have been approved for fludeoxyglucose F18 injection, for a total of three different indications. FDA expects that applicants will seek approval of fludeoxyglucose F 18 injection for three approved indications, using either the 505(b)(2) NDA route to approval or the ANDA approval route as appropriate.

[15] See footnote 13.

[16] Because NDAs are subject to user fees while ANDAs are not, an applicant seeking to reduce its user fee liability could consider modifying its product so that it is eligible for approval under an ANDA.

2. Ammonia N 13 injection

There is an approved NDA for ammonia N 13 injection. We expect that applicants will seek approval of ammonia N 13 injection for the approved indication using either the 505(b)(2) NDA route to approval or the ANDA approval route as appropriate. Although Ammonia N13 injection is covered by new chemical entity exclusivity, the NDA holder has waived the exclusivity and therefore applications may be submitted at this time.

3. Sodium fluoride F 18 injection

There are two approved NDAs for sodium fluoride F 18 injection (NDA 17-042 and NDA 22-494). Both are listed in the "Discontinued Drug Product List" section of the Orange Book. However, FDA has determined that neither drug was withdrawn from sale for reasons of safety or effectiveness, and therefore they may be referenced in marketing applications. Accordingly, you can submit an ANDA for sodium fluoride F 18 if your product is ***the same as*** either RLD. You can also submit a 505(b)(2) NDA if your product formulation differs from the RLD in certain ways and the proposed changes do not affect previous findings of safety and effectiveness (see Section V.C. and Appendix B).

If you have any questions about the type of application you should submit or about application requirements for other PET drugs or for other possible indications for the three PET drugs discussed in this guidance, please contact the Division of Medical Imaging Products (DMIP) in the Center for Drug Evaluation and Research (CDER).

V. WHAT ELSE SHOULD YOU KNOW ABOUT SUBMITTING AN APPLICATION?

It is important to become familiar with the application form, *Form FDA 356h*. A sample format for Form FDA 356h is included on our web site for each PET drug addressed in this guidance.[17] This form may be used for both NDAs and ANDAs.[18] Appendices A and B walk you through Form FDA 356h section by section for an NDA and ANDA, respectively.

This section describes briefly some of the documents you will be asked about in Form FDA 356h and provides some additional information you may find useful.

A. Can I Submit the Application Electronically?

[17] See CMC Sample Formats at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078743.pdf.

[18] Form FDA 356h is available on FDA's web site at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/default.htm.

NDAs and ANDAs may be submitted either electronically or in paper format. However, electronic submissions are preferred because they facilitate FDA's review of the application.[19] Therefore, we recommend that electronic submissions use the Common Technical Document (CTD) format. A paper format may prove most feasible if you lack the technical support to develop an electronic submission.

If you proceed to develop an electronic submission, we encourage you to obtain a pre-assigned application number and a secure email account with FDA, as described at the following web site: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm114027.htm

The CTD format is designed to minimize the potential for omission of critical information through the use of five components (Modules 1 through 5) that contain information applicable to the items listed on page 2 of Form FDA 356h.[20] The following will be useful in explaining expectations for the CTD format:

- Guidance *Submitting Marketing Applications According to the ICH/CTD Format: General Considerations*
- Guidance *ICH M2 EWG: Electronic Common Technical Document Specification*
- Guidance *ICH M4: Organization of the CTD*
- Submit a sample eCTD to help verify the technical feasibility of your plans: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm.

If you decide to submit your application electronically, please note that FDA will consider as *technically deficient* and *not received* any electronic application that is not submitted in an electronic format that can be processed, reviewed, and archived.[21]

We anticipate an NDA or ANDA will contain predominantly chemistry, manufacturing, and controls (drug quality) information. Within the CTD, the drug quality information is provided in Module 3. Information to include in this module is described in the guidance document titled, *M4Q: The CTD — Quality*.[22]

Submission of the sample eCTD should help minimize the potential for technical deficiencies and provide an opportunity for you to obtain feedback from the FDA technical review staff.

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[19] For more on electronic submissions, see guidance for industry *Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163556.pdf.

[20] The sample formats have been kept in the old Office of Generic Drugs format to avoid confusion for the three commonly used drugs which are the subject of this guidance. You may organize the application in the CTD format and keep the CMC sections (module 3 of the CTD format) for these drugs in the format indicated in the sample formats. Alternatively, you can organize the application, including CMC, in CTD format. Module 3 is essentially the same for both NDAs and ANDAs.

[21] See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072385.pdf

[22] See http://www.fda.gov/RegulatoryInformation/Guidances/ucm129901.htm.

Questions regarding the electronic submission process may be directed to esub@fda.hhs.gov.

B. Labeling

Whether submitting an NDA or ANDA, you will be required to submit labeling for the drug product to FDA. *Labeling* is a collective term and for PET drug products consists of:

- Prescribing Information (which contains a summary of the essential information needed for the safe and effective use of the product);
- Label for the drug vial; and
- Label for the lead storage container.

When submitting the NDA or ANDA, the content of the drug labeling must be submitted to FDA electronically using the Structured Product Labeling (SPL) format. For the three drugs discussed in this guidance, FDA has provided labeling templates in SPL on our website that you can use whether you are submitting an NDA or ANDA.[23] The templates contain most of the required labeling information and cannot be modified. You may reference these templates in your application but must separately provide required information in SPL that is specific to your products (e.g., name and address of manufacturer). Further instructions and information on SPL and free software that may be used to submit information in SPL is available on FDA's website.[24]

- Ammonia N 13 injection and fludeoxyglucose F 18 injection labeling templates are consistent with the 2006 final rule concerning the new requirements for prescribing information for drug and biological products.[25] These regulations revised the content and format of the prescribing information of new drugs to make information more accessible and easier to read and use.

- NDA 17-042 for sodium fluoride F 18 injection was approved prior to implementation of the final rule on the new requirements for prescribing information, and the labeling has not been updated to address dosage and usage information. On our website, we provide both the older approved labeling as well as newer formatted text. If you intend to submit an ANDA referencing NDA 17-042, you should use the older approved labeling. If you submit an NDA or an ANDA referencing NDA 22-494, you should use the newer labeling template which has information presented in the new required format. We will recommend any necessary changes during our review. Labeling for NDA 22-494, Sodium Fluoride F-18 Injection, is consistent with the 2006 final rule on prescribing information and can be found at Drugs@FDA.[26]

[23] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm241316.htm.
[24] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.
[25] See 21 CFR 201.56 and 201.57
[26] See http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022494Orig1s000lbl.pdf.

Additional information regarding the content and format of the prescribing information is available on the FDA website: *New Requirements for Prescribing Information*.[27]

If you are submitting an ANDA, your labeling will be the same as the NDA RLD labeling. If, for example, you intend to propose different pediatric dosing, you would have to submit studies to justify the change. This type of change could not be made in an ANDA and would require submission of a 505(b)(2) application.

FDA recognizes that PET drugs are frequently distributed outside the normal channels of distribution for drugs. However, PET producers are responsible for distributing labeling to the end user. At this time, we recommend that the labeling be made available at some specific location or website to which the end user may be referred.

C. Bioequivalence

If your proposed PET drug product is the same Qualitatively (Q1 = same ingredients) and Quantitatively (Q2 = same amounts of the inactive ingredients with a + or – 5% difference), you can request a waiver under 21 CFR 320.22 of any requirement for evidence of in vivo bioequivalence (BE). Specific language to request a waiver is provided in the ANDA (generic drug) section of this guidance.

If the proposed product is not Q1 and Q2 the same (as discussed above), the product's bioequivalence must be demonstrated in accordance with 21 CFR 320.24. For intravenously administered PET drug products, in accordance with 21 CFR 320.24(b)(6), FDA has determined that bioequivalence has been demonstrated in cases where differences in the inactive ingredients are sufficiently small that they will not significantly affect the physical and chemical properties of the drug product and where such ingredients have been previously used in the same or greater quantities in an approved drug product for the same route of administration.

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 (see 21 CFR 314.94(a)(9)(iii)) in the proposed PET drug product, where such ingredients and their amounts have been previously approved in a drug product and their amounts do not affect physical or chemical properties (e.g., specific gravity, viscosity, pH) in relation to the RLD.

- Presence of or absence of a preservative, buffer or an antioxidant (see 21 CFR 314.94(a)(9)(iii)) in the proposed PET drug product, where such a 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.

[27] See http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

To demonstrate bioequivalence under 21 CFR 320.24(b)(6), the application should include a discussion with supportive evidence, usually from the FDA list of inactive ingredients in previously approved products, to support that the proposed product differences from the RLD are not likely to affect the safety or efficacy of the product.[28]

D. Patents

If you submit an NDA for a PET drug product (including a 505(b)(2) NDA), you must also submit information on each patent that claims the drug or a method of using the drug (that is the subject of the NDA). Such patents consist of drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method of use patents.[29]

FDA has created two forms to facilitate the listing of patents in the Orange Book, FDA form 3542a and FDA form 3542. FDA form 3542a must be submitted in an original NDA to alert the Agency to your intent to list patents for your product. Form 3542 must be submitted within 30 days of the approval of an NDA. Form 3542 will be used by the Orange Book staff to list any patents for your approved product. Both of these forms have a checkbox to indicate when an applicant does not intend to list any patents. Therefore, these forms should be submitted even if you have no patents to list.

If you submit an NDA under 505(b)(2) of the Act or an ANDA, you must provide a certification with respect to each patent that is listed in the Orange Book, which claims the RLD.[30] For each such patent, you must provide the patent number and certify one of the following circumstances:

- That the patent information has not been submitted to FDA (*Paragraph I Certification*);
- That the patent has expired (*Paragraph II Certification*);
- The date on which the patent will expire (*Paragraph III Certification*); or
- That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted (*Paragraph IV Certification*).

Please see the Appendices for further information about patents and patent certifications. Information about patents claiming drugs that have been approved is available in the *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)* at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

E. What is a Drug Master File?[31]

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[28] See http://www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm

[29] See 21 CFR 314.53.

[30] See 21 CFR 314.54(a)(1)(vi) and 314.94(a)(12).

[31] For additional information about DMFs, see the Guideline for Drug Master Files available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073164.htm and the DMF web page available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm.

A *drug master file*, also known as a DMF, is a file that usually contains information about a drug substance, a component, or a container/closure system that is proprietary (i.e., belongs to someone else). This information may not be available to you,[32] but you may need it as part of your NDA or ANDA. Rather than providing the information directly to you and to everyone who uses their product, the manufacturer may choose to hold a DMF. The DMF holder provides the information directly to FDA.

If a manufacturer holds a DMF that you would like to reference, you should ask them to provide you with a letter of authorization (see below), which you must include with (and reference in) your application and list on your Form FDA 356h.

A DMF could contain information required in an application about the following areas:

- Drug substance, drug substance intermediate, and materials used in their preparation, or drug product (Type II);
- Packaging materials (Type III);
- Excipient, colorant, flavor, essence, or materials used in their preparation (Type IV); or
- FDA accepted reference information (Type V).

If you intend to reference a DMF, we will need a letter of authorization from the DMF holder granting FDA authorization to refer to information in its DMF during the review of your application. The letter of authorization should be on the DMF holder's letterhead and dated and signed with an original signature. The letter should cite the DMF holder's name, drug name, and DMF number.

If, for example, you want to rely on DMF information concerning the bulk drug substance, the authorization must be granted by the holder of the DMF for each source of bulk drug substance. If the letter of authorization is made by a third party (i.e., another corporate entity, agent, or supplier), the DMF holder should provide the authorization to the third party giving the authority to grant referrals to the DMF.

For PET drugs, the manufacturers of automated synthesis equipment may submit a Type V DMF that addresses the following:

- Equipment description and principle of operation
- Equipment specifications
- Quality system information
- Design Controls
- Performance standards essential requirements
- Design verification testing including programming logic / software testing
- Safety margin testing
- Equipment shelf-life

[32] The regulatory requirements for a DMF are found in 21 CFR 314.420.

- Risk assessment including Failure Mode, Effects and Criticality Analysis (FMECA)
- Functional and electrical testing
- Bench testing including extraneous environment testing.
- Data for performance verification studies
- Results of USP extractable study per chapter <381> and USP biological reactivity as per chapter <87> and chapter <88> on elastomeric components that come in contact with the drug

F. What About Foreign Documents?

Foreign publications or documents can be submitted to FDA as part of your application (e.g., as part of your chemistry section). If you submit foreign publications or documents, you must also provide English translations of this information with the application.[33]

[33] See 21 CFR 314.50(g).

APPENDIX A: NDAs — WHAT SHOULD YOU INCLUDE IN YOUR NDA?

This Appendix is based extensively on section 505(b) of the Act and regulations in 21 CFR part 314. As a result, this section contains extensive mandatory language. This mandatory language is used whenever FDA regulations require the submission of certain information. Unlike other guidance documents in which mandatory language is typically accompanied by the related cite, to make the guidance more user friendly and less cumbersome, we do not cite each regulation each time we discuss a requirement.

Once you have decided to submit an NDA, you must fill out application Form FDA 356h and provide the Agency with a variety of information on your product. The information published in the PET Safety and Effectiveness Notice will form the basis for approval of 505(b)(2) NDAs for the three PET products discussed in this guidance.

After providing general information about NDA submissions, we will walk you through the application, explaining what you should put in each section of your application. Incorporate these sections into the module (1 through 5) components of the CTD format.

When an NDA is submitted to FDA as a paper submission, three copies are required: (1) an archival copy for the official record, (2) a review copy to be used to evaluate your application, and (3) a field copy, which will be used as part of your preapproval inspection by the FDA. We will describe the specific requirements for the field copy later in this guidance.

You should send your completed paper application to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging Products (DMIP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you choose to supply your application electronically, submit via the electronic submission gateway, as described in section V.A.[34]

An NDA submission generally consists of an *application form* and a *series of individual sections*.

A. Application Form

The application form is Form FDA 356h. This form must be completed and signed by the applicant or responsible official.

[34]CDER's specifications for submitting applications on physical and electronic media, including CDs are available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163567.pdf.

The form contains seven major sections: (1) applicant information, (2) product description, (3) application information, (4) establishment information, (5) the individual items based on the regulations, (6) certification, and (7) signature of responsible official. Each of these sections is discussed in detail in the following paragraphs.

1. Applicant information

This section requests general information about the applicant: name, address, telephone number, and fax number. If you wish to use an agent or consultant to act on your behalf, you should also provide the name and address of the person authorized on your behalf in the application. If a particular section does not apply, please write "NA" (not applicable).

2. Product description

Below is a template that can be adapted for use in the Product Description section of Form FDA 356h:

Template for product descriptions

Established Name:	Fludeoxyglucose F 18 injection (or ammonia N 13 injection or sodium fluoride F 18 injection)
Proprietary Name*:	Indicate proprietary name (or write "none")
Dosage Form:	Injection
Strengths:	Indicate amount of drug substance range in mCi/mL at end of synthesis (EOS) calibration time
Route of Administration:	Intravenous

*We do not anticipate the need for proprietary names. If you wish to propose a proprietary name, information on the proposal submission process is available in FDA guidance.[35]

Supply a previously assigned application number within the designated space on the form.

3. Application description

This section asks for information about the *type of application* you are submitting.

- You should check the appropriate application type in the first box (NDA).

[35] See Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf.

- In the next box, you should identify that you are submitting a 505(b)(2) type of NDA.
- In the box for ANDAs, you should write "NA".
- Under Type of Submission, you should check the appropriate type. For the three drugs addressed in this guidance, you will most likely check Original Application.
- Under Reason for Submission, you should write "Complete new application that has never before been submitted."
- Under Proposed Marketing Status, you should check Prescription Product (Rx).
- You should check the appropriate boxes to identify the number of volumes submitted and the application format.

4. Establishment information

You should supply the requested information; if you need more space, attach an additional sheet.

In the next part, on Cross References, you may want to reference other applications in your application. For example, you may refer to an investigational new drug application (IND), an NDA or ANDA, or a drug master file (DMF). If you reference another application or a DMF, you should list the number(s) of the referenced documents in this Cross References section.

5. The individual items based on the regulations

This is the longest, most detailed part of Form FDA 356h. The individual items in this section are discussed in detail in section B below.

6. Certification

This section is at the end of Form FDA 356h following the individual items. It provides your certification to FDA that the information you are providing is true to the best of your knowledge. You also agree to update specific parts of your application as needed and submit required safety reports. Finally, the certification shows that you agree to comply with all applicable laws and regulations.

- Current good manufacturing practices

As directed by section 121 of FDAMA, FDA has developed CGMP requirements for PET drugs (74 FR 65409, December 10, 2009). These requirements are set forth in 21 CFR part 212 and become effective December 12, 2011. In the future, Form FDA 356h will be changed to reflect the PET drug industry's need to comply with the regulations in part 212. Until then, you should provide the following statement in your application:

(Name of Applicant) *certifies that the methods used in and the facilities and controls used for the compounding, manufacturing, processing, packaging, testing, and holding of* (name of drug) *conform and will continue to conform to the positron emission tomography compounding standards and the official monographs of the United States Pharmacopeia until December 12, 2011. As of December 12, 2011, the methods used in and the facilities and controls used for the compounding, manufacturing, processing, packaging, testing, and holding of* (name of drug) *will conform to the requirements in 21 CFR 212.*

7. Signature of responsible official

After reading and understanding the information provided in the Certification section, the responsible official is asked to sign the application and provide some additional routine information.

B. Individual Items in the Application Form

The following discussion addresses the individual items in an NDA as they appear on page 2 of Form FDA 356h and is based on the specific requirements in the regulations (21 CFR 314.50). Each item is discussed, and recommendations are made as to what information should be included in the application. These items may be submitted in the CTD format, with incorporation of each item into its applicable module. Administrative information, the index, and labeling are included within module 1. Other module contents are designated within each item.

All applicants should follow the list of items on page 2 of Form FDA 356h as they complete their applications. This list, which corresponds to the following discussion, identifies what should be included and should be used as a road map for organizing and locating information in the application. See also the suggested formats for Form FDA 356h in the separate attachments.

1. Index

You should provide an index for your submission. If you submit in a paper format, the individual sections of the application (i.e., the items in this list) and each section of each volume, if applicable, should be separated by dividers and tabbed. Pages should be numbered sequentially from the first page in volume one to the last page in the last volume (i.e., each volume should not start with page one).

2. Labeling

The draft package insert must be submitted electronically, regardless of whether your NDA is paper-based or entirely electronic. Other aspects of electronic labeling submission are described in section V.B.

Within a paper-based submission, the application must also contain four (4) copies of a draft product label and all labeling for the drug product. See section V.B. for information about submitting labeling electronically.

Once FDA approves your NDA, you will need to submit the final content of labeling (package insert) electronically. The final vial and lead container labels may be submitted electronically or as paper copies. If you submit paper copies of the vial and container labels, supply 12 copies.[36]

3. Summary

You must provide a summary of your application (module 2 of the CTD). The summary can be a simple statement naming the drug product, listing the indication(s), and stating your reliance on the PET Safety and Effectiveness Notice, which provides the basis for the determination of safety and effectiveness required for FDA approval. *Here is an example of an application summary for* fludeoxyglucose F 18 injection *for all three indications*:

> *In accordance with FDA's PET Safety and Effectiveness Notice published in the Federal Register of March 10, 2000 (65 FR 12999), (*Name of applicant*) is submitting this new drug application, as described in section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, for fludeoxyglucose F 18 injection for the following indications:*
>
> 1. *Fludeoxyglucose F 18 injection is indicated in positron emission tomography (PET) imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.*
>
> 2. *Fludeoxyglucose F 18 injection is indicated in positron emission tomography (PET) imaging in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function.*
>
> 3. *Fludeoxyglucose F 18 injection is indicated in positron emission tomography (PET) imaging in patients for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.*

[36] See 21 CFR 314.50(e)(2)(ii)

Here is an example of an application summary for ammonia N 13 injection:

> *In accordance with FDA's PET Safety and Effectiveness Notice published in the Federal Register of March 10, 2000 (65 FR 12999),* (Name of applicant*) is submitting this new drug application, as described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for ammonia N 13 injection. Ammonia N 13 injection is indicated for positron emission tomographic (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease.*

Here is an example of an application summary for sodium fluoride F 18 injection:

> *In accordance with FDA's PET Safety and Effectiveness Notice published in the Federal Register of March 10, 2000 (65 FR 12999),* (Name of applicant*) is submitting this new drug application as described in section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, for sodium fluoride F 18 injection. Sodium fluoride F 18 injection is indicated for positron emission tomography (PET) imaging as a bone imaging agent to define areas of altered osteogenic activity.*

4. Chemistry section

We have provided as separate attachments on our web site sample formats for chemistry sections (that can be submitted in CTD module 3) for each of the three PET drug products addressed in this guidance.[37] You can use these sample formats to provide information and data in your application about your manufacture of these PET drugs.

5.-12. Sections 5 through 12

You will not need to supply much information for these sections. Within Module 4 (nonclinical study reports), you may designate the section as "not applicable" if you are relying on the PET Safety and Effectiveness Notice as the basis for the determination of safety and effectiveness required for FDA approval of your NDA for fludeoxyglucose F 18 injection, sodium fluoride F 18 injection, or ammonia N 13 injection. You should provide a statement referencing the notice (CTD Module 5). In addition, you must provide a pediatric assessment indicating the requirement has been satisfied, waived, or deferred, as appropriate, as required by the Pediatric Research Equity Act (PREA) Public Law 108-155 (2003) (codified at 21 U.S.C. 355B). These are discussed below, and sample statements are provided.

[37] Module 3 of the CTD includes both a drug substance and a drug product section. If the drug substance and drug product in your application are the same, you need only provide the information once. You may, however, provide information about the precursor in the drug substance section.

Here is an example of a statement referring to the PET Safety and Effectiveness Notice as the basis for your NDA. Please fill in the name of the appropriate PET drug.

> *For this NDA for* (name of drug*), information requirements for the following sections are satisfied by the PET Safety and Effectiveness Notice published in the Federal Register of March 10, 2000 (65 FR 12999):*
>
> *Clinical pharmacology and toxicology*
> *Human pharmacokinetics and bioavailability*
> *Clinical data*
> *Safety update report*
> *Statistical section*
> *Case report tabulations*
> *Case report forms*
>
> *The PET Safety and Effectiveness Notice states that FDA will consider the evidence for approval of this PET drug to include FDA's determination of safety and effectiveness for the indications stated above.*

- Pediatric Research Equity Act (PREA)

PREA requires that all applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain an assessment of the safety and effectiveness of the drug for the claimed indication in relevant pediatric subpopulations unless the requirement is waived or deferred. Among the three PET drugs and indications discussed in this guidance, safety and effectiveness have been established among pediatric patients in all relevant age groups for ammonia N 13 injection, for sodium fluoride F 18 injection, as well as for the neurologic use (epilepsy) of fludeoxyglucose F 18 injection.

The pediatric use of fludeoxyglucose F18 injection for the oncology and cardiac indications has not been established. If you submit an NDA for all three fludeoxyglucose F 18 injection indications, include a statement that describes your plans to address the need for pediatric assessments in all relevant pediatric age groups. We suggest that you include the following statements to address the pediatric assessment expectations within an NDA.

Within an NDA for ammonia N 13 injection, sodium fluoride F 18 or fludeoxyglucose F 18 injection (neurologic indication):

> The PET Safety and Effectiveness Notice states that there is sufficient information for pediatric assessment in the labeling of (name of PET drug) for the indications listed in the notice in all relevant pediatric age groups.

Within an NDA for fludeoxyglucose F18:

The PET Safety and Effectiveness Notice states that the pediatric assessment for sodium fluoride F 18 injection is deferred for five years until the agency adopted approval procedures and CGMP requirements. A five year deferral is also requested for the oncologic and cardiac indications for fludeoxyglucose F 18 injection.

13.-14. Patent Certification and Exclusivity Statement

Applicants submitting 505(b)(2) NDAs must submit information regarding the patent protections covering and exclusivity sought for the PET product for which approval is sought and patent certifications and exclusivity statements regarding patents or exclusivity covering the listed drug they reference. More information on these two topics and examples of the statements you will need to provide in your application are provided here. This information is provided within CTD module 1.

Protections covering the PET product for which approval is sought:

- Patent information

Any applicant who submits an NDA must provide the Agency with the patent number and expiration date for patents, held by the applicant or anyone else, for certain patents (21 CFR 314.53). Specifically, information must be submitted for patents covering the drug product (formulation, composition), the drug substance (active ingredient), or a method of use for which the applicant seeks approval, such as a drug product's indication for use.[38]

Prior to approval, applicants must use FDA form 3542a to submit information on these patent(s) to the Agency. After an NDA is approved, the applicant must confirm the patent(s) to be listed by submitting FDA form 3542 within 30 days of approval. These forms must be used even when the applicant has no patents to list.[39]

After approval, the applicant will be required to submit relevant patent information for patents that claim the approved drug substance, drug product, or method of use on form 3542.

- Claimed exclusivity

FDA can grant 3- or 5-year marketing exclusivity for certain drug products approved through the NDA process.[40] For example, 5 years of marketing exclusivity are granted by FDA for new chemical entities that have never been previously approved by FDA alone or in combination.

[38] Process patent information must not be submitted to FDA (21 CFR 314.53(b)). When the application is approved, patent information will be published in the *Orange Book*.
[39] This form is available on the Internet at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.
[40] See 21 CFR 314.108.

Three-year exclusivity may be granted if new clinical studies are conducted by or for the applicant and are essential to the approval of an NDA or a supplement to an NDA, such as for approval or a new indication. Because we anticipate no need for you to submit clinical study data, an exclusivity claim is not likely to be appropriate for NDAs and ANDAs submitted in accordance with this guidance. NDA applicants who believe they are eligible for either 3- or 5-year exclusivity must include in the NDA information describing the basis for the claimed exclusivity.[41]

Protections covering other approved NDAs for the same PET drug:

- Patent certifications

Applicants submitting 505(b)(2) NDAs are required to submit patent certifications for the patents listed for the listed drug their application references.[42] If you seek to reference fludeoxyglucose F 18 injection, sodium fluoride F 18 injection, or ammonia N 13 injection and no patents are listed for the drug in the *Orange Book* at the time of your submission, you need only provide a *no relevant patents certification.*[43]

Here is an example of a *no relevant patents certification* statement that you can use for fludeoxyglucose F 18 injection, sodium fluoride F 18 injection, or ammonia N 13 injection:

> *In the opinion and to the best knowledge of* (name of applicant), *there are no patents that claim the listed drug or that claim a use of the listed drugs.*

In the future, when additional applications for these PET drug products are approved, the patent status of these PET drugs could change. Patent information should be verified with the latest version of the *Orange Book* (published and updated electronically) and its supplements.

- Exclusivity statement

The submission and approval of 505(b)(2) NDAs may be affected by exclusivity granted to an approved product. Fludeoxyglucose F 18 injection, and sodium fluoride F 18 injection are approved PET drug products and currently ***are not covered*** by any market exclusivity. Because they are not covered by any market exclusivity, you should provide a *no exclusivity statement* in your NDA.[44] Here is an example of a *no exclusivity statement* you can use in your NDA for fludeoxyglucose F 18 injection or sodium fluoride F 18 injection.

[41] See 21 CFR 314.50(j).
[42] Additional information about patent certifications can be found in 21 CFR 314.50(i).
[43] See 21 CFR 314.50(i)(1)*(ii)*.
[44] See 21 CFR 314.107(d).

According to the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), the reference listed drug is not subject to a period of marketing exclusivity under section 505(c)(3)(E) of the Act (21 U.S.C. 355(c)(3)(E)).

Ammonia N 13 injection is covered by NCE exclusivity. However, the NDA holder has waived the exclusivity.[45] Here is an example of a statement you can use for Ammonia N 13 in your NDA until August 23, 2012, when the exclusivity for Ammonia N 13 injection expires. After that time, the *no exclusivity* statement may be used in your NDA for Ammonia N 13.

[Name of applicant] *acknowledges the New Chemical Entity (NCE) exclusivity attached to NDA 022119. This exclusivity expires on August 23, 2012. However, as indicated in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), the holder of NDA 022119, Feinstein Institute Medical Research, has waived this exclusivity. Because NCE exclusivity for NDA 022119 has been waived,* [Name of applicant] *may submit an NDA for Ammonia N 13 prior to the expiration of NCE exclusivity.*

In the future, when additional applications for these PET drug products are approved, the exclusivity status of these PET drugs could change. Exclusivity information should be verified with the latest information in the *Orange Book* and its supplements.

15. Establishment description

This item on Form 356h does not apply to drug applications submitted to the Center for Drug Evaluation and Research.

16. Debarment certification

You must provide a debarment certification and a conviction statement. Explanations and examples are provided below.

- Debarment certification

As of June 1, 1992, an NDA must include certification that the applicant did not and will not use the services (in any capacity) of any person debarred under section 306(a) or (b) of the Act (21 U.S.C. 355a(a) or (b)) in connection with the submission of their application.[46]

[45] See *Approved Drug Products with Therapeutic Equivalence Evaluations* (*Orange Book*) available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[46] Use of a debarred individual or firm may preclude the approval of the application.

Debarment is an administrative procedure used by the Agency to bar individuals and/or companies who have been convicted of a felony or a misdemeanor related to the development or approval of any drug from providing certain services to an applicant or manufacturer. Typically, a debarred person is an individual or company convicted of fraud related to the submission of a drug application.

Debarment certification is a self-attestation by the applicant. Applicants must include a certification addressing debarment and a statement about conviction of crimes that could lead to debarment. Here is an example of a debarment certification that you can use in your NDA.

> *I,* (name of applicant*), certify that I, or we, did not and will not use the services, in any capacity, of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.*

- Convictions

No information or statement with respect to convictions is needed if your application is an NDA.

17. Field copy certification

The field copy of your NDA will be used by FDA field investigator(s) during your PET drug production facility's preapproval inspection. The field copy must contain the NDA's *technical section*, the *application form*, and the *summary***.** You must certify that it is a true copy of the technical section described in the regulations and contained in the archival and review copies of the application.

Here is an example of a field copy certification you can use.

> (Name of applicant*) certifies that the field copy is a true copy of the technical section of the application described in 21 CFR 314.50(d)(1) and contained in the archival and review copies of the application.*

If questions arise regarding the field copy, please contact CDER's Office of Compliance at 301-796-3100

18. User fee cover sheet (Form FDA 3397)

For NDAs:

- Complete the PDUFA user fee cover sheet online at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm. Detailed instructions are provided on the Web page.
- In response to the question asking if you have a waiver, answer "Yes" if your 505(b)(1) or (b)(2) application was submitted in accordance with the PET Safety and Effectiveness Notice.

- When you have answered all questions, review the form for accuracy.

- Submit the form electronically for assignment of a user fee ID number. Print the final cover sheet with the assigned user fee ID number.

- Include a signed copy of the cover sheet with the assigned user fee ID number with Form FDA 356h in the NDA.

19. Financial Disclosure Information

Because the determination of safety and effectiveness for these PET drugs is based on the Agency's review of the literature or on previous Agency findings regarding approved applications, rather than on clinical trials to support the submission of an application, it is not necessary to include a financial disclosure form (Form FDA 3455) with these applications. For this same reason, financial certifications and disclosure statements by clinical investigators (21 CFR part 54) are *not required* as part of the applications for fludeoxyglucose F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection.

APPENDIX B: ANDAS — WHAT SHOULD YOU INCLUDE IN YOUR ANDA?

This section of the guidance is based largely on section 505(j) of the Act and regulations in 21 CFR part 314, subpart C. As a result, this section contains extensive mandatory language. This mandatory language is used whenever the Act and/or FDA regulations require the submission of certain information. Unlike other guidance documents in which mandatory language is typically accompanied by the related cite, to make the guidance more user friendly and less cumbersome, we do not cite each regulation each time we discuss a requirement.

This section of the guidance discusses the content and format of an ANDA. If your drug is *the same as* a listed drug (e.g., fludeoxyglucose F 18 injection, sodium fluoride F 18 injection, or ammonia N 13 injection), you should submit an ANDA. After providing general information, we will present a step-by-step description of what you should put in each section of the ANDA. Sample formats for the content and format of the chemistry sections for each PET drug are provided as separate attachments.

Before beginning to fulfill the submission requirements of the ANDA, you should determine whether your product is the same as the listed drug you reference (RLD). As noted in section IV.B., some minor differences are permitted.

Once you have decided to submit an ANDA, you must fill out Form FDA 356h and provide the FDA with a variety of information on your product. An ANDA contains a completed and *signed application form* (Form FDA 356h) and a number of *individual items* based on the regulations.

When an ANDA is submitted to the FDA, three copies are required if the application is paper-based: (1) an archival copy for the official record, (2) a review copy to be used to evaluate your application, and (3) a field copy, which will be used as part of your preapproval inspection by the FDA. The archival copies are to be submitted in blue jackets, the review copies are to be submitted in red jackets, and the field copies are to be submitted in burgundy jackets. We will describe the specific requirements for the field copy later in this guidance.

If submitting a paper application, your completed application should be sent to:

Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

If you choose to submit your application electronically, you may submit it via the electronic submission gateway, or you may submit it electronically on physical media. See http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163567.pdf. If you are submitting through the gateway, organize the submission in the CTD format, in a manner similar to that for an NDA.

A. Application Form

The application form is Form FDA 356h.[47] This form should be completed and signed by the applicant, or the responsible official.

The form contains seven major sections: (1) applicant information, (2) product description, (3) application description, (4) establishment information, (5) the individual items based on the regulations, (6) certification, and (7) signature of responsible official. These sections are discussed in detail in the following paragraphs.

1. Applicant information

This section requests general information about the applicant: name, address, telephone number, and fax number. If you wish to use an agent or consultant to act on your behalf, you should also provide the name and address of the person authorized on your behalf in the application. If a particular section does not apply, please write "NA" (not applicable).

2. Product description

The descriptions below should be used in completing this section for these three PET drugs:

Product description template for use in PET drug application

Established Name:	Fludeoxyglucose F 18 injection (or sodium fluoride F 18 injection)
Proprietary Name:	Write "none" or identify the proposed proprietary name*
Dosage Form:	Injection
Strengths:	Indicate amount of drug substance range in mCi/mL at end of synthesis (EOS) reference time
Route of Administration:	Intravenous
Indication(s) for use:	As in Section III (above)

[47] This form contains the information required under 21 CFR 314.94(a)(1) for an ANDA.

*We do not anticipate the need for proprietary names. If you wish to propose a proprietary name, information on the proposal submission process is available in FDA guidance.[48]

3. Application description

This section asks for information about the *type of application* you are submitting.

- You should check the appropriate application type in the first box (ANDA).
- You should write "NA" in next box and go to the third box.

In this box, you are asked to provide general information on the RLD. An ANDA must state the name of the RLD including its dosage form and strength as identified by the symbol (+) in the *Approved Drug Products With Therapeutic Equivalence Evaluations* (the *Orange Book*).

For fludeoxyglucose F 18 injection, the RLD should be listed as one of the following:

NDA 20-306, Fludeoxyglucose F 18 Injection, held by Downstate Clinical PET Center

NDA 21-768, Fludeoxyglucose F 18 Injection, held by Weill Medical College of Cornell University

NDA 21-870, Fludeoxyglucose F 18 Injection, held by Feinstein Institute for Medical Research

NDA 21-768, Fludeoxyglucose F 18 Injection, held by Weill Medical College of Cornell University

NDA 21-870, Fludeoxyglucose F 18 Injection, held by Feinstein Institute for Medical Research

[48] See Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names. This guidance is located at the internet address of: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf.

Note: If FDA approves other applications for fludeoxyglucose F 18 injection submitted in accordance with the PET Safety and Effectiveness Notice, it is possible that these products could become alternative RLDs.

For sodium fluoride F 18 injection, the RLD should be listed as one of the following:

> *NDA 17-042, (18 F) as Fluoride Ion in Saline Solution, held by GE Healthcare.*

> *NDA 22-494, Sodium Fluoride F-18 Injection, held by the National Cancer Institute.*

> *NDA 22-494, Sodium Fluoride F-18 Injection, held by the National Cancer Institute.*

For ammonia N 13 injection, the RLD should be listed as follows:

> *NDA 22-119, Ammonia N 13 injection, held by Feinstein Institute for Medical Research*

As with fludeoxyglucose F 18 injection, if FDA approves other applications for sodium fluoride F 18 injection or ammonia N 13 injection submitted in accordance with the PET Safety and Effectiveness Notice, it is possible that these products could become alternative RLDs.

- Under Type of Submission, you should check the appropriate type. For the drugs addressed here, you will most likely check Original Application.
- Under Reason for Submission, you should write "Submission of an ANDA."
- Under Proposed Marketing Status, you should check Prescription Product (Rx).

4. Establishment information

Supply the requested information; if you need more space, attach an additional sheet.

5. Cross References

You may want to reference other applications in your ANDA which contain information upon which you want to rely. For example, you may refer to an investigational new drug (IND),

NDA, or other ANDA, or a drug master file (DMF). If you are going to reference another application or DMF, you should list the number(s) of the referenced documents in this section.

6. The individual items based on the regulations

This is the longest, most detailed part of Form FDA 356h. The individual items in this section are discussed in detail in section B, below. The items required for an ANDA differ from those on page 2 of Form FDA 356h. Please use the list presented in section B as the proper list of individual items to be submitted (see also http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064995.htm).

7. Certification

This section is at the end of Form FDA 356h following the individual items. It provides your certification to the FDA that the information you are providing is true to the best of your knowledge. You also agree to update specific parts of your application as needed and submit required safety reports. Finally, the certification states that you agree to comply with all applicable laws and regulations.

- Current good manufacturing practices

As directed by section 121 of the Modernization Act, the FDA has developed current good manufacturing practice (CGMP) requirements for PET drugs (74 FR 65409, December 10, 2009). These requirements are set forth in 21 CFR part 212 and become effective on December 12, 2011. In the future, Form FDA 356h will be changed to reflect the PET drug industry's need to comply with the regulations in part 212. Until then, you should provide the following statement in your application:

> (Name of Applicant) *certifies that the methods used in and the facilities and controls used for the compounding, manufacturing, processing, packaging, testing, and holding of* (name of drug) *conform and will continue to conform to the positron emission tomography compounding standards and the official monographs of the United States Pharmacopeia, until December 12, 2011. As of December 12, 2011, the methods used in and the facilities and controls used for the compounding, manufacturing, processing, packaging, testing and holding of* (name of drug) *will conform to the requirements in 21 CFR 212.*

8. Signature of responsible official

After reading and understanding the information provided in the Certification section, the responsible official is asked to sign the application and provide some additional routine information.

B. Individual Items in the Application

The following discussion addresses the individual items in an ANDA. Rather than providing the items listed on page 2 of Form FDA 356h, some of which apply only to NDAs, you should provide information to FDA according to the list that follows here. Each of the following items is discussed and recommendations are made as to what information should be included. The following discussion is based on the specific requirements in the regulations (21 CFR 314.94) and section 306(k) of the Act.

An ANDA contains the following individual items or sections:

1. Table of contents
2. Basis for ANDA submission (reference to listed drug or approved suitability petition)
3. Patent certification and exclusivity statement
4. Comparison of RLD and generic drug
   - Conditions of use
   - Active and inactive ingredients
   - Route of administration, dosage form, and strength
5. Bioequivalence information
6. Labeling
7. Chemistry, manufacturing, and controls information
8. Financial disclosure
9. Debarment certification
10. Field copy certification
11. Other

This list, which corresponds to the following discussion, identifies what should be included and can be used as a road map for organizing the application. In addition, we have prepared sample formats for the chemistry sections for the PET drug products addressed in this guidance, available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078740.pdf

1. Table of contents

All ANDAs should include a table of contents following Form FDA 356h. The current recommended format for submitting an ANDA is the CTD. Applications in CTD format may be submitted to the Agency in either paper CTD or electronic CTD format. For information regarding the organization of an ANDA in CTD format, see the ANDA checklist for CTD or eCTD format, which is available at the Office of Generic Drugs Web page at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm142112.htm. The eleven items listed in this section should be organized in a manner that corresponds to the modules of the CTD, as indicated in the ANDA checklist.

The table of contents provides a road map to locate information in the application. Each section of the application should be delineated by dividers and tabbed when submitted in paper, and the pages should be numbered sequentially from the first page in volume one to the last page in the last volume (i.e., each volume should not start with page 1).

2. Basis for ANDA submission (RLD)

You should cite the RLD you will be using in the application as described above under Application Description.

3. Patent Certification and exclusivity statements

You will need to submit both a patent certification and an exclusivity statement. Examples are provided here.

- Patent certification

ANDA applicants are required to submit patent certifications. The need for patent certifications depends on the patents listed for the RLD in the *Orange Book*.[49]

Currently, there are no patents listed in the *Orange Book* for the approved PET drugs, fludeoxyglucose F 18 injection, sodium fluoride F 18 injection, or ammonia N 13 injection. If at the time of ANDA submission there are no listed patents for your RLD, you must provide a *no relevant patents certification* in your ANDA.

Here is an example of a *no relevant patents certification* that you can use for fludeoxyglucose F 18 injection, sodium fluoride F 18 injection, and ammonia N 13 injection, as long as no patents are listed.

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

- Exclusivity statement

The submission and approval of ANDAs may be affected by exclusivity granted to the RLD.[50] Fludeoxyglucose F 18 injection and sodium fluoride F 18 injection are approved PET drugs and currently are *not covered* by any market exclusivity. If at the time of ANDA submission they are not covered by any market exclusivity, you should provide an *exclusivity statement* in your ANDA acknowledging that there is no unexpired exclusivity for the RLD.[51]

[49] Additional information about patent certifications can be found in 21 CFR 314.94(a)(12).
[50] See 21 CFR 314.108(b).
[51] See 21 CFR 314.94(a)(3)(ii).

Here is an example of an *exclusivity statement* you can use for fludeoxyglucose F 18 injection and sodium fluoride injection in your ANDA.

> According to the *Approved Drug Products with Therapeutic Equivalence Evaluations* (*Orange Book*), the reference listed drug is not entitled to a period of marketing exclusivity under Section 505(j)(5)(F) of the Act (21 U.S.C. 355(j)(5)(F)).

Ammonia N 13 injection is covered by exclusivity, however, the NDA holder has waived the exclusivity.[52] Here is an example of a statement you can use for Ammonia N 13 in your ANDA.

> [Name of applicant] *acknowledges the New Chemical Entity (NCE) exclusivity attached to NDA 022119. This exclusivity expires on August 23, 2012. However, as indicated in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), the holder of NDA 022119, Feinstein Institute for Medical Research, has waived this exclusivity. Because NCE exclusivity for NDA 022119 has been waived,* [Name of applicant] *may submit an ANDA for Ammonia N 13 prior to the expiration of NCE exclusivity.*

In the future, when additional applications for these PET drug products are approved, the patent or exclusivity status could change and other patent and/or exclusivity statements could be required. Patent and exclusivity information always should be verified with the latest information in the "Patent and Exclusivity Addendum" of the *Orange Book* and its supplements.

4. Comparison of RLD to generic drug

This is the section in which you should provide information comparing your drug (the generic drug) to the RLD you are referencing. You will be asked to provide information on the conditions of use, active and inactive ingredients, route of administration, dosage form, and strength.

Following a brief discussion of each, an example statement is provided in the box at the end of this section along with tables showing comparisons of the proposed generic with the RLD for fludeoxyglucose F 18 injection, sodium fluoride F 18 injection, and ammonia N 13 injection.

- Conditions of use

[52] See *Approved Drug Products with Therapeutic Equivalence Evaluations* (*Orange Book*) available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

You should provide a statement that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the drug product have been previously approved for the RLD. In the statement, indicate that you have provided the necessary information in the labeling section of the application (see example statements below).

- Active and inactive ingredients

ANDA submission requires that the proposed generic drug be the same as the RLD, with certain exceptions discussed below. *Same* means that the proposed drug has identical active ingredient(s), dosage form, strength, route of administration, and conditions of use as the RLD, and is bioequivalent to the RLD. Generic injectable drug products can differ from the RLD in preservative, buffer, and/or antioxidant (exception excipients). These differences must not affect the safety or effectiveness of the generic drug.

You should provide a statement that the active ingredient in the proposed drug product is the same as the active ingredient in the RLD. In the statement, indicate that you have provided the necessary information in the labeling section of the application (see example statements below). Examples of ways in which the generic product may differ from the RLD include:

- The generic product may include a permissible exception excipient that does not appear in the RLD provided the difference does not affect the safety or effectiveness of the product.
- The generic product may omit an exception excipient that is present in the RLD provided the difference does not affect the safety or effectiveness of the product.
- The concentration of the exception excipient in the generic product may be different from that in the RLD, but has been previously approved in another drug product given by the same route of administration (e.g., intravenous). The difference must not affect the safety or effectiveness of the product.

If the inactive ingredients in a generic PET injectable drug product differ from the RLD in ways other than those described in the bulleted list above, an ANDA may not be appropriate. In such cases, a 505(b)(2) NDA might be appropriate.

- Route of administration, dosage form, and strength

You must provide a statement that the route of administration, dosage form, and strength of the proposed drug product are the same as those of the RLD (see example statements below).[53] Here is a statement you can use if your product is the same as the RLD in active ingredient, conditions of use, route of administration, dosage form, and strength.

[53] Any differences require an approved *suitability petition*.

The conditions of use prescribed, recommended, or suggested in the labeling proposed for the generic drug have been previously approved for the RLD.

The active ingredient, route of administration, dosage form, and strength are the same as that of the RLD.

If differences exist between your proposed drug and the RLD and you have obtained approval of an ANDA suitability petition (see section IV.B.3.), these differences should be explained and a copy of the suitability petition approval letter should be included.

The tables below compare a proposed drug with the RLD for fludeoxyglucose F 18 injection, sodium fluoride F 18 injection, and ammonia N 13 injection, respectively. You can adapt these tables and insert the appropriate table into your application under Comparison of RLD and generic drug.

Comparison of proposed generic fludeoxyglucose F 18 injection with the RLD

	Generic Drug	**RLD**
Conditions of use:	1. Fludeoxyglucose F 18 injection is indicated in positron emission tomography (PET) imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer. 2. Fludeoxyglucose F 18 injection is indicated in positron emission tomography (PET) imaging in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function. 3. Fludeoxyglucose F 18 injection is indicated in positron emission tomography (PET) imaging in patients for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.	1. Fludeoxyglucose F 18 injection is indicated in positron emission tomography (PET) imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer. 2. Fludeoxyglucose F 18 injection is indicated in positron emission tomography (PET) imaging in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function. 3. Fludeoxyglucose F 18 injection is indicated in positron emission tomography (PET) imaging in patients for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.
Active ingredient:	2-Deoxy-2[^{18}F]fluoro-D-glucose	2-Deoxy-2[^{18}F]fluoro-D-glucose
Route of administration:	Intravenous	Intravenous

Dosage form:	Injection	Injection
Strength:	4 – 90 mCi/mL (EOS*) or 10 – 100 mCi/mL (EOS*) or 20 – 200 mCi/mL (EOS*)	4 – 90 mCi/mL (EOS*) or 10 – 100 mCi/mL (EOS*) or 20 – 300 mCi/mL (EOS*)

*End of synthesis calibration time

Comparison of proposed generic sodium fluoride F 18 injection with the RLD

	Generic Product	**RLD**
Conditions of use:	Sodium fluoride F 18 Injection is indicated for diagnostic positron emission tomography (PET) imaging of bone to define areas of altered osteogenic activity.	Sodium fluoride F 18 Injection is indicated for diagnostic positron emission tomography (PET) imaging of bone to define areas of altered osteogenic activity
Active ingredient:	Sodium fluoride F 18	Sodium fluoride F 18
Route of administration:	Intravenous	Intravenous
Dosage form:	Injection	Injection
Strength:	10 – 200 mCi/mL at EOS (end of synthesis)	10 – 200 mCi/mL at EOS (end of synthesis)

Comparison of proposed generic ammonia N 13 injection with the RLD

	Generic Product	**RLD**
Conditions of use:	Ammonia N 13 injection is indicated for diagnostic positron emission tomography imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease.	Ammonia N 13 injection is indicated for diagnostic positron emission tomography imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease.
Active ingredient:	Ammonia N 13	Ammonia N 13
Route of administration:	Intravenous	Intravenous
Dosage form:	Injection	Injection
Strength:	3.75-37.5 mCi/mL (EOS)	3.75-37.5 mCi/mL (EOS)

5. Labeling

The term product labeling is a collective term that includes the package insert, vial labels, and lead container labels. The contents of labeling must be submitted electronically, regardless of whether you submit a completely electronic or paper-based application. See section V.B. for information about submitting labeling electronically. If your application is paper-based, you must also submit four (4) copies of a draft product label and all proposed labeling for the drug product.

You must submit a statement that your proposed labeling is the same as the labeling for the RLD except for any differences annotated and explained. If you reference the labeling templates on FDA's web site, you will incorporate by reference the appropriate information and you will not need to provide a side-by-side comparison.

If you do not reference the labeling templates on FDA's web site, you also need to include a side-by-side comparison of your package insert and container labels with the RLD with all differences annotated and explained. The labeling for approved drugs is available online at Drugs@FDA and the National Library of Medicine (see http://dailymed.nlm.nih.gov/dailymed).

Once FDA approves your ANDA, you will need to electronically submit the final content of labeling (package insert). The final vial and lead container labels may be submitted electronically or as paper copies. If you submit paper copies of the carton and container labeling, supply 12 copies.

6. Bioequivalence

This section of the application should include a side-by-side comparison of the formulation of the proposed generic drug and the RLD. Below are examples of side-by-side comparisons for each drug that you can adapt to your application.[54]

If your injectable product is identical to the RLD, containing the same active and inactive ingredients in the same concentrations (inactive ingredient variability of +/-5% is allowed), you can request a *waiver* under 21 CFR 320.22 of any requirement for evidence of in vivo bioequivalence. In this case, bioequivalence will be established based on other data in the application. You should request a waiver using the following language:

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

If the proposed product is not Q1 and Q2 the same (as discussed above), the product's bioequivalence must be demonstrated in accordance with 21 CFR 320.24. For intravenously administered PET drug products, in accordance with 21 CFR 320.24(b)(6), FDA has determined that bioequivalence has been demonstrated in cases where differences in the inactive ingredients are sufficiently small that they will not significantly affect the physical and chemical properties of the drug product and where such ingredients have been previously used in the same or greater quantities in an approved drug product for the same route of administration.

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 (see 21 CFR 314.94(a)(9)(iii)) in the proposed PET drug product, where such ingredients and their amounts have been previously approved in a drug product and their amounts do not affect physical or chemical properties (e.g., specific gravity, viscosity, pH) in relation to the RLD.
- Presence of or absence of a preservative, buffer or an antioxidant (see 21 CFR 314.94(a)(9)(iii)) in the proposed PET drug product, where such a change does not affect tonicity (osmolality) of the solution in relation to the RLD or an applicant has established that the change in tonicity will not affect safety or effectiveness of the product.

To demonstrate bioequivalence under 21 CFR 320.24(b)(6), the application should include a discussion with supportive evidence, usually from the FDA list of inactive ingredients for

[54] As noted in section IV.B. this refers to a comparison between the end products.

previously approved products to support that the proposed product differences from the RLD are not likely to affect the safety or efficacy of the product.[55]

Fludeoxyglucose F 18 injection: side-by-side comparison (applicant to fill in missing information)

Description	RLD	Applicant's Proposed Drug Product
Active Ingredient: 2-Deoxy-2-[^{18}F]fluoro-D-glucose	4 mCi to 90 mCi/mL @ EOS* or 10 mCi to 100 mCi/mL @ EOS* or 20 mCi to 300 mCi/mL @ EOS*	_?_ mCi to _?_ mCi/mL @ EOS*
Inactive Ingredients: Sodium chloride injection, USP (Sodium chloride in WFI) or Sodium chloride , Citrate (in water for injection (WFI)	9 mg/mL 4.5 mg/mL 7.2 mg/mL	_?_ mg/mL
Osmolality	List from package insert of RLD	_____
Specific Activity	No carrier added	?
Dosage form	Injection	Injection
Route of Administration	Intravenous	Intravenous

Sodium fluoride F 18 injection: side-by-side comparison (applicant to fill in missing information)

Description	RLD NDA 22-492	Applicant's Proposed Drug Product
	10 – 200 mCi/mL at EOS (end of synthesis)	_?_ mCi/ mL to _?_ mCi/mL @ EOS
Inactive Ingredients: 0.9% Sodium chloride solution	9 mg/mL	_?_ mg/mL
Specific Activity	No carrier added	?
Dosage form	Injection	Injection
Route of Administration	Intravenous	Intravenous

[55] See http://www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm

Description	RLD NDA 17-042	Applicant's Proposed Drug Product
Active Ingredient: Sodium Fluoride F18	2 mCi / mL @ calibration (4.22 – 0.22 mCi / mL)	__?__ mCi/mL @ calibration (__?__ - __?__ mCi/mL)
Inactive Ingredients: Sodium chloride injection, USP (Sodium chloride in WFI)	9 mg/mL	__?__ mg/mL
Specific Activity	No carrier added	?
Dosage form	Injection	Injection
Route of Administration	Intravenous	Intravenous

Ammonia N 13 injection: side-by-side comparison (applicant to fill in missing information)

Description	RLD	Applicant's Proposed Drug Product
Active Ingredient: Ammonia N 13	3.75 mCi to 37.5 mCi/mL @ (EOS)*	__?__ mCi to ? mCi/mL @ (EOS)*
Inactive Ingredient: 0.9% aqueous sodium chloride	9 mg/mL	__?__ mg/mL
Specific Activity	No carrier added	?
Dosage form	Injection	Injection
Route of Administration	Intravenous	Intravenous

* End of synthesis

7. Chemistry section

Sample formats for chemistry sections for each of these PET drugs are available on FDA's web site at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078740.pdf
You may use these sample formats to provide information and data regarding your manufacture of these PET drugs.

8. Financial disclosure

It is not necessary to include a financial disclosure form (Form FDA 3455) with an ANDA unless the application contains an in vivo bioequivalence study.

9. Debarment certification

The regulations require submission of a debarment certification and a conviction statement. Explanations and examples are provided below.

- Debarment certification

As of June 1, 1992, any ANDA must include certification that the applicant did not and will not use the services (in any capacity) of any person debarred under section 306(a) or (b) of the Act in connection with the submission of their application.[56]

Debarment is an administrative procedure used by the FDA to bar an individual and/or company convicted of a felony or a misdemeanor related to the development or approval of any drug from providing certain services to an applicant or manufacturer. Typically, a debarred person is an individual or company convicted of fraud related to the submission of a drug application.

Debarment certification is a self-attestation by the applicant. You simply need to include a certification addressing debarment and conviction of any crimes that could lead to debarment.

Here is an example of a debarment certification that you can use in your NDA.

> *I,* (name of applicant*), certify that I, or we, did not and will not use the services, in any capacity, of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.*

- Convictions

All ANDAs should include a nonconviction statement or, if necessary, they must include information about any convictions (of the company or affiliated persons) of relevant offenses, i.e., felonies or misdemeanors related to the development or approval of any drug that could have led to debarment.[57]

If you or anyone else who is responsible for the development or submission of the ANDA has not been convicted of a relevant offense within the last 5 years, a simple statement to that effect should be submitted.

Here is an example of a nonconviction statement that you can use.

> (Name of applicant*) did not and will not use the services, in any capacity, of anyone convicted of a relevant offense within the last 5 years in connection with this application.*

If you or an affiliated person responsible for the development or submission of your application has a conviction(s) of a relevant offense that could lead to debarment and that conviction

[56] Use of a debarred individual/firm may preclude the approval of the application.
[57] See 21 U.S.C. 335a.

occurred within 5 years before the date of the application, you must include a list of these convictions. The list of convictions should include the following information:

- The name(s) of the person and/or firm convicted
- The title of the section of the Federal or State statute involved
- The date of the conviction
- The sentencing date
- The court entering judgment
- The case number, if known
- A brief description of the offense

In addition, the applicant should explain the role of each convicted person in the development of the application. The debarment certification and conviction information should be signed by a responsible officer of the applicant or by an individual responsible for signing the application.

10. Field copy certification

The field copy of your ANDA will be used by FDA field investigator(s) during your PET center's preapproval inspection. The field copy should contain the *technical section*, the *application form*, and the *summary.* You must certify that it is an exact copy of the information contained in the review copy of the application.

Here is an example of a field copy certification you can use.

> (Name of applicant*) certifies that the field copy is a true copy of the technical section of the application described in 21CFR 314.50(l)(3) and contained in the archival and review copies of the application.*

If questions arise regarding the field copy, please contact the Pre-Approval Manager in your home FDA district office.

11. Other

- *User Fees*

Currently, fees do not apply to 505(j) applications. You do not need to fill out the user fee cover sheet.

APPENDIX C: FORMS

The following sample formats are available as separate documents on FDA's Web site.

I. Sample formats for chemistry, manufacturing, and controls sections

Fludeoxyglucose F 18 Injection
Ammonia N 13 Injection
Sodium Fluoride F 18 Injection

Are available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078740.pdf

II. Sample formats for Form FDA 356h:

Fludeoxyglucose F 18 Injection
Ammonia N 13 Injection
Sodium Fluoride F 18 Injection

Are available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078743.pdf

Sample formats for labeling of Fludeoxyglucose F 18 Injection, Ammonia N 13 Injection and Sodium Fluoride F 18 Injection are available on FDA's SPL web site at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm241316.htm.