Guidance for Industry

PET Drug Applications — Content and Format for NDAs and ANDAs

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of the draft document contact Robert K. Leedham, Jr., 301-827-7510.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
March 2000
Procedural

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For additional copies contact the:

Drug Information Branch
Division of Communications Management, HFD-210
5600 Fishers Lane, Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
or
http://www.fda.gov/cder/regulatory/pet/default.htm

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I. INTRODUCTION

This guidance is intended to assist applicants in preparing new drug applications (NDAs) or abbreviated new drug applications (ANDAs) for fludeoxyglucose (FDG) F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection used in positron emission tomography (PET) imaging. 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).[2]

This guidance provides (1) brief background information, (2) information that should help you decide whether you should submit an NDA or an ANDA, (3) a complete description of the content and format needed in an NDA and an ANDA, and (4) boxed text that you can copy or cut and paste into your application. The content and format sections provide all the information required in the submission of an NDA or an ANDA for these PET drug products. Finally, we have developed sample formats for the content and format for the chemistry sections and for the proposed labeling for FDG F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection. We also are providing sample applications and user fee cover sheets. The attachments are not included in the guidance, but are being made available separately.

We recommend that applicants follow the directions described in this guidance to avoid unnecessary expenditure of time, effort, and resources in preparing their applications.

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[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. This guidance document represents the Agency's current thinking on the content and format of NDAs and ANDAs for certain positron emission tomography (PET) drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

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

Because this guidance discusses in great detail what *must be* submitted in a 505(b)(2) NDA or an ANDA, the guidance differs from most guidances in that it contains extensive mandatory language, especially in sections VII and VIII. This mandatory language is used whenever 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. WHY IS THE FDA REGULATING PET DRUGS?

On November 21, 1997, President Clinton signed into law the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115; Modernization Act). Section 121(c) of the Modernization Act directs FDA to regulate PET drugs. Section 121 identifies a number of tasks for the FDA with specific time frames, including

- The FDA must develop appropriate procedures for the approval of PET drugs as well as current good manufacturing practice (CGMP) requirements for such drugs.

- The FDA is to 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.

- The FDA cannot require the submission of NDAs or ANDAs for compounded PET drugs that are not adulterated as described in the Act for a period of 4 years after the date of enactment or 2 years after the date the 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.

III. WHAT HAS THE FDA BEEN DOING TO MEET THE NEW REQUIREMENTS?

Since November 1997, the FDA has been working to implement section 121 of the Modernization Act. The Agency has conducted several public meetings with various representatives of the Institute for Clinical PET (ICP), an industry trade association, 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, the FDA decided to conduct its own review of the published literature.[3] The FDA's goal was to evaluate the safety and effectiveness of the PET drugs in

[3]As stated in FDA guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (May 1998), the 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.

widespread use for certain indications and to facilitate the process of submitting applications for these products for the PET drug industry.

The FDA reviewed the literature and evaluated the studies of safety and effectiveness for several commonly used PET drug products for previously unapproved indications, including FDG F 18 injection for oncology and for assessing myocardial viability, and ammonia N 13 injection for assessing myocardial blood flow. The Agency discussed its preliminary findings on the safety and effectiveness of these drugs for these indications with the ICP and other interested persons at public meetings. On June 28-29, 1999, the Agency presented its findings to its Medical Imaging Drugs Advisory Committee (Advisory Committee). The Advisory Committee concluded that FDG 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 the FDA.

IV. WHAT ARE THE FDA'S FINDINGS?

Based on its literature review and findings and the recommendations of the Advisory Committee, the FDA has developed the basis for the approval of NDAs and ANDAs for FDG F 18 injection and ammonia N 13 injection for certain indications (see list below). The Agency's findings regarding the already approved NDAs for PET drugs and indications are the basis for approval of FDG F 18 injection for the foci of epileptic seizures and of sodium fluoride F 18 injection for the bone imaging indication (see starred indications in the list below).[*]

In a notice in the *Federal Register* in March 2000 (the PET Safety and Effectiveness Notice),[4] the FDA presented its findings of safety and effectiveness for certain PET drugs for certain indications. The PET Safety and Effectiveness Notice describes the types of applications that can be submitted for the following PET drugs for the indications listed here.

Fludeoxyglucose F 18 Injection (FDG F 18)

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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

[*] Starred indications have been approved in previous PET NDAs.

[4] The *Federal Register*, March __, 2000, vol. 65, p._____. See also FDA's PET Internet page at http://www.fda.gov/cder/regulatory/pet/default.htm.

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.

Ammonia N 13 Injection

1. 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.

Sodium Fluoride F 18 Injection

*1. 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.

Based on the FDA's findings, published in the PET Safety and Effectiveness Notice, and on the FDA's prior approvals of some of these PET drugs, if you are producing these PET drugs for the above stated indications, you are not required to conduct studies or submit new safety and effectiveness information to obtain approval for these products. You need only reference in your marketing application the published literature and/or FDA's determination of safety and effectiveness for these drugs in accordance with the PET Safety and Effectiveness Notice.

V. WHAT KIND OF AN APPLICATION SHOULD YOU SUBMIT?

An applicant seeking approval for a PET drug may submit an NDA or an ANDA, depending on the specific drug and the indications for which approval is sought. NDAs for the PET drugs discussed in section IV of this guidance are of the type described in section 505(b)(2) of the Act, which generally rely for approval on references to studies conducted by others and/or on published literature. Applicants submitting 505(b)(2) NDAs for PET drugs can rely on the FDA's review of the literature as described in the PET Safety and Effectiveness Notice and/or on previous approvals of PET drugs for certain indications.[5]

* Starred indications have been approved in previous PET NDAs.

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

An *ANDA* is usually submitted for a drug product that is *the same as* a drug product previously approved by the FDA. When an applicant submits an ANDA based on a previously approved product, the previously approved drug product is known as the *reference listed drug* (RLD),[6] and the proposed product that is the same as the RLD is called the *generic drug*.

FDA regulations (21 CFR 314.92) define *the same as* to mean a generic drug has the *identical active ingredient(s), dosage form, strength, route of administration, and conditions of use* as its RLD.[7] If your proposed drug differs from the RLD in certain ways, you can still submit an ANDA. You probably will have to submit a *suitability petition* first, which could lengthen the time it takes for your application to be approved. Unless your product is identical to one of the RLDs, you should probably submit a 505(b)(2) NDA. The ways in which generic drugs are allowed to differ from the RLD and the appropriate situations for submitting suitability petitions are discussed in more detail in sections VI.E. and VIII.

Because there are approved NDAs for FDG F 18 injection and sodium fluoride F 18 injection for specific indications (the starred indications in the list in the previous section), 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 indication) or an NDA (if your product is different from the already approved product and/or you are seeking approval for all three listed indications). The FDA expects that most applicants will seek approval of FDG F 18 injection for all three indications.

Because there is no approved NDA for ammonia N 13 injection at this time, the FDA can accept only NDAs for that PET drug product based on the Agency's findings in the PET Safety and Effectiveness Notice. Once an application for ammonia N 13 injection has been approved, it most likely will become the RLD, and applicants will be able to submit ANDAs based on the RLD.

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

A. FDG F 18 injection

An NDA has been approved for FDG F18 injection for one of the three indications listed here. However, the FDA expects that most applicants will seek approval of FDG F 18 injection for all three indications, using the 505(b)(2) NDA route to approval. Once an NDA for these three indications has been approved, you can use the ANDA approval route.

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[6] 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)). The FDA lists approved drugs that may be referenced in an ANDA in the *Approved Drug Products With Therapeutic Equivalence Evaluations* (the *Orange Book)*.

[7] See 21 CFR 314.94(a)(5)(i)(A) and (a)(6)(i)(A).

B. Ammonia N 13 injection

Currently, the FDA can accept *only NDAs* for ammonia N 13 injection because there is no approved NDA for this PET drug product. This would likely be a 505(b)(2) application based on the PET Safety and Effectiveness Notice. Once there is an approved NDA for ammonia N 13 injection, that product will probably become the RLD for the approval of subsequent ANDAs for ammonia N 13 injection.

C. Sodium fluoride F 18 injection

There is an approved NDA for sodium fluoride F 18 injection for the listed indication. Therefore, you can submit an ANDA for this drug if your product is *the same as* the RLD, or a 505(b)(2) NDA if your product differs (see sections VI.E and VIII for more information on what changes are permitted).

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 and Radiopharmaceutical Drug Products at 301-827-7510.

VI. WHAT ELSE DO YOU NEED TO KNOW ABOUT SUBMITTING AN APPLICATION?

Before we begin an in depth discussion of what goes into NDAs and ANDAs, you should first become familiar with the application, *Form FDA 356h*. A sample format for FDA 356h has been included as a separate attachment for each PET drug addressed in this guidance. This form can be modified for both NDAs and ANDAs.[8] Sections VII and VIII of this guidance 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 other information you may find useful.

A. What is a drug master file?

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,[9] but you may need it as part of your NDA or ANDA. The chemistry section of Form FDA 356h may ask you to provide this information. This information is usually available from the supplier or manufacturer of the subject of the DMF.

[8] Form FDA 356h is available on the Internet at http://forms.psc.gov/forms/fdaforms/fdaform/html.
[9] The regulatory requirements for a DMF are found in 21 CFR 314.420.

Rather than providing the information directly to you and to everyone that uses their product, the manufacturer may choose to *hold a DMF*. The DMF holder provides the information directly to the 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 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)
- FDA accepted reference information (Type V)

B. What are letters of authorization?

If you want to *reference a DMF*, we will need a letter of authorization from the DMF holder granting the FDA authorization to refer to information in their 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.

If you wish to use an agent or consultant to act on your behalf, we recommend that you provide the name and address of the person authorized on your behalf in your application.

C. What about foreign documents?

Foreign publications or documents can be submitted to the 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.[10]

D. What is a sample statement?

[10] 21 CFR 314.50(g)(2).

At some time during the application process, the FDA may request that you provide representative samples. Generally, when the FDA asks for a representative sample, it is a sample of the drug product proposed for marketing, the drug substance or components used in the manufacturing of the drug product, or the reference standards. If the Agency makes such a request, it will state specifically what materials are requested, how to provide the representative sample, and any additional information that is needed. If you are asked to provide a sample of material, you must include a statement with the requested material.

E. What is a suitability petition?

As discussed in the previous section, an applicant can submit an *ANDA* to the FDA for a drug product that is *the same as* a drug product previously approved by the FDA. Because NDAs for FDG F 18 injection and sodium fluoride F 18 injection already have been approved, it is possible for you to submit an ANDA for a PET product that is the same as one of these two drugs (see discussion in section VIII). FDA regulations (21 CFR 314.92) define *the same as* to mean the generic drug has *the identical* active ingredient(s), dosage form, strength, route of administration, and conditions of use as the RLD. Certain changes from the RLD are permitted, however.

If your product differs (see the product descriptions in section VIII) from the RLD in any of the ways listed in the box below, you can still submit an ANDA, but you will be required to submit a suitability petition to obtain permission to file an ANDA with such a change.[11]

Table 1: Permitted changes that will require a suitability petition

- Strength
- Route of administration
- Dosage form

If you have any questions about submitting an ANDA or about suitability petitions, please contact the Office of Generic Drugs at 301-827-5845.

[11] 21 CFR 314.93. A suitability petition could lengthen the time it takes to approve an application. There is an approved ANDA suitability petition for FDG F 18 injection that involves changes in strength, including mCi/mL, total activity and total drug content, from the reference listed drug (Docket No. 97P-0432/CP1).

F. Is it possible to make an electronic submission?

In February 1999, the Agency announced that it was able to accept NDAs in electronic format. To assist applicants who wish to submit an electronic NDA, the FDA developed and issued two guidances explaining how best to assemble an electronic NDA. Both of these guidances, *Providing Regulatory Submissions in Electronic Format — General Considerations* (January 1999) and *Providing Regulatory Submissions in Electronic Format — NDAs* (January 1999), are available on the Internet and from the Drug Information Branch.

It is also possible to submit parts of an ANDA in electronic format. For more information, see the FDA's *Preparing Data for Electronic Submission in ANDAs* (September 1999).

For more information on electronic submissions and electronic reviews, see the following site on the FDA Web page: http://www.fda.gov/cder/regulatory/ersr/default.htm.

VII. NDAS — WHAT SHOULD YOU INCLUDE IN YOUR NDA?

This section of the guidance is based extensively on section 505(b) of the Act and regulations in 21 CFR Subpart B. 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 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.

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 Agency's March 2000 PET Safety and Effectiveness Notice,[15] will form the basis for approval of 505(b)(2) NDAs for the three PET products discussed here.

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. Sample formats for applications have been included as separate attachments. Please refer to the sample formats for further guidance. In most sections, boxed text is provided that can be copied into your application.

When an NDA is submitted to the FDA, 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 application to:[16]

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Rm. 2-14
12420 Parklawn Dr.
Rockville, MD 20857

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

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[15] The *Federal Register*, March __, 2000, vol. 65, p._____. See also FDA's PET Internet page at http://www.fda.gov/cder/regulatory/pet/default.htm.

[16] The FDA can now accept NDAs in electronic format (see previous discussion of electronic submissions).

A. Cover Letter

The application should include a signed and dated cover letter with a clear, brief introductory statement. The cover letter should be on the applicant's letterhead stationery. The cover letter should contain the following information:

- ***Purpose of the application*** (to obtain approval of an NDA to market (Name of PET drug) for (list indications)) stated above

- ***Type of submission*** (your application will probably be a 505(b)(2) NDA)

- ***Name, title, signature, and address of the applicant***. The *applicant* is any person who submits an application or an abbreviated application. It also includes any person who owns an approved application or an abbreviated application. Usually, the name, title, signature, and address of the applicant belong to a *responsible official*. Typically, commercial manufacturers have an employee in the regulatory affairs department submit an application on their behalf. This person serves as the *responsible official.*

- ***Established name and proprietary name (if any)*** for the proposed drug product. It is not necessary to provide a proprietary or trade name for these three PET drug products in your application. However, the established name is required. The established name is often referred to as the *generic name* of a drug product. For the PET drug products in this guidance, the established names are (1) fludeoxyglucose F 18 injection, (2) ammonia N 13 injection, and (3) sodium fluoride F 18 injection.

- ***Number of volumes submitted.*** Depending on the size of your application, you may want to divide the application into separate volumes for easier handling.

B. Application Form

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

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 a particular section does not apply, please write "NA" (not applicable).

2. Product description

The following table shows an example of a product description that can be used in the Product Description section of Form FDA 356h for these three PET drugs:

Table 2: Example of 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) reference time
Route of Administration:	Intravenous

3. Application information

This section asks for information about the *type of application* you are submitting (NDA or ANDA).[17]

- Please check the appropriate application type in the first box (NDA).
- In the next box, identify that you are submitting a 505(b)(2) type of NDA.
- In the box for ANDAs, write "NA."
- Under Type of Submission, check the appropriate type. For the three drugs addressed in this guidance you will most likely check Original Application.
- Under Reason for Submission, write "Complete new application that has never before been submitted."

[17] BLA (for biological drug products being submitted to the Center for Biologics Evaluation and Research) does not apply to these PET drugs.

- Under Proposed Marketing Status, check Prescription Product.

4. Establishment information

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 C below.

6. 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 shows 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 is developing current good manufacturing practice (CGMP) requirements for PET drugs. In the future, Form FDA 356h will be changed to reflect the PET drug industry's need to comply with PET current good manufacturing practice regulations. Until then, 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.*

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.

C. 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.

All applicants should follow the list of items on page 2 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. Also, see the suggested formats for Form FDA 356h in the attachments. We have prepared a sample NDA application for each of the PET drug products addressed in this guidance.

1. Index

Provide an index for your submission. The individual sections of an 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 application must contain four (4) copies of a draft product label and all labeling for the drug product. The term *product labeling* is a collective term that includes the package insert, vial labels, and carton labeling. Sample formats for product labeling for each of the PET drugs addressed in this guidance have been included as separate attachments. These sample formats contain all the necessary information for submitting product labeling and can easily be adapted to your specific application. See the attachments for sample formats for labeling for FDG F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection.

Once the FDA approves your NDA, you will need to submit 12 copies of the final printed labeling (also known as FPL) to the FDA as part of your official records. Copies of the final printed labeling are sent to various FDA offices as part of the approval process.

3. Summary

You should provide a summary of your application. 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 *FDG F 18 injection* for all three indications:

> *In accordance with the FDA's PET Safety and Effectiveness Notice, (*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. FDG 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. FDG 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. FDG 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.*

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

> *According to the FDA's PET Safety and Effectiveness Notice,* (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*:

> *According to the FDA's PET Safety and Effectiveness Notice,* (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 sample formats for chemistry sections for each of the three PET drug products addressed in this guidance. You can use these sample formats to provide information and data in your application about your manufacture of these PET drugs.

If questions arise on the Chemistry Section, please contact the Division of Medical and Radiopharmaceutical Drug Products in the Center for Drug Evaluation and Research at (301) 827-7510.

5.-12. Sections 5 through 12

You will not need to supply much information for these sections. You need to provide a statement referring to the PET Safety and Effectiveness Notice as the basis for the determination of safety and effectiveness required for FDA approval of your NDA for FDG F 18 injection, sodium fluoride F 18 injection, or ammonia N 13 injection. In addition, you need to provide a statement on pediatric assessments. Both are discussed below, and sample statements are provided.

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:*
>
> *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 assessments are usually required for new active ingredients, new dosage forms, new dosing regimens, new formulations, new routes of administrations, and new indications.[18] At this time, however, for the PET products and indications addressed in this guidance, you need only include a statement similar to the statements below.

Here is an example of a statement on pediatric assessment for FDG F 18 injection and ammonia N 13 injection. Please fill in the name of the appropriate PET drug.

> *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.*

[18] 21 CFR 314.50(d)(7); 21 CFR 314.55

The statement for sodium fluoride F 18 injection is a little different. Here is an example of a statement on pediatric assessment for sodium fluoride F 18 injection:

> *The PET Safety and Effectiveness Notice states that the pediatric assessment for sodium fluoride F 18 injection is deferred at this time.*

13.-14. Patent Certification and Exclusivity Statement

Applicants submitting 505(b)(2) NDAs must submit information regarding the patent and exclusivity protections covering the PET product for which approval is sought, and patent certifications and exclusivity statements regarding patents or exclusivity covering an approved NDA for the same drug. More information on these two topics and examples of the statements you will need to provide in your application are provided here.

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, related to the drug product.[19] Information must be submitted for patents covering the drug product (formulation, composition), the drug substance (active ingredient), or the method of use, such as a drug product's indication for use.[20] Patents covering the formulation, composition, or method of use must be accompanied by the following signed declaration:

> *The undersigned declares that Patent No. _____ covers the formulation, composition, and/or method of use of* (name of drug product)*. This product is (currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act) [or] (the subject of this application for which approval is sought).* (signature)

- Claimed exclusivity

[19] 21 CFR 314.53

[20] Process patent information should not be submitted to the FDA. When the application is approved, patent information will be published in the *Orange Book*.

The FDA can grant 3- or 5-year marketing exclusivity for certain drug products approved through the NDA process.[21] For example, 5 years of marketing exclusivity are granted by the FDA for new chemical entities. 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 a new indication. 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.[22]

Protections covering other approved NDAs for the same PET drug:

- Patent certifications

Applicants submitting 505(b)(2) NDAs are required to submit patent certifications. The need for patent certifications depends on the patents listed in the *Orange Book* for approved NDAs for the same drug.[23] Because FDG F 18 injection and sodium fluoride F 18 injection currently ***are not covered*** by patents listed in the *Orange Book*, you need only provide a *no relevant patents certification.*[24]

Here is an example of a no relevant patents certification statement that you can use for FDG F 18 injection and sodium fluoride F 18 injection:

> *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.*

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 information in the "Patent and Exclusivity Information Addendum" of the *Orange Book* 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.[25] Here is an example of a no exclusivity statement you can use in your NDA for FDG F 18 injection or sodium fluoride F 18 injection:

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[21] See 21 CFR 314.108

[22] See 21 CFR 314.50(j)

[23] Additional information about patent certifications can be found in 21 CFR 314.50(i).

[24] 21 CFR 314.50(i)(1)(ii)

[25] See 21 CFR 314.107(d).

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

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 "Patent and Exclusivity Information Addendum" of 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.[26]

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. You simply need to 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.*

[26] Use of a debarred individual or firm may preclude the approval of the 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 center's preapproval inspection. The field copy should contain the NDA's *chemistry section*, the *application form*, and the *summary***.** You must certify that it is an exact copy of the information 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 the Office of Compliance in the Center for Drug Evaluation and Research at (301) 594-0054.

18. User fee cover sheet (Form FDA 3397)

For NDAs:

- Obtain a user fee cover sheet (Form FDA 3397 - rev 5/98) (see sample format in attachments).[27]
- Complete boxes 1 through 4 and 6 (skip 5 and 7).
- Check Yes for box 8 and note that the application fee was waived in accordance with the PET Safety and Effectiveness Notice
- Sign and date the form.
- Include the cover sheet with Form FDA 356h.

[27] The User Fee Cover Sheet can be obtained from the Internet. The web address is www.fda.gov/cder/pdufa/default.htm. Click on the subject "Other" and one of the options will be "User Fee Cover Sheet."

19. Other

- Financial Disclosure

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. In addition, financial certifications and disclosure statements by clinical investigators (21 CFR part 54) are *not required* as part of the applications for FDG F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection.

- Sample statement

At some time during the application process, the FDA may request that you provide representative samples. Generally, when the FDA asks for a representative sample, it is a sample of the drug product proposed for marketing, the drug substance or components used in the manufacturing of the drug product, or the reference standards. If the Agency makes such a request, it will state specifically what materials are requested, how to provide the representative sample, and any additional information that is needed. If you are asked to provide a sample of material, you must include a statement with the requested material.

Here is an example of a sample statement.

Upon request of the FDA, (Name of applicant*) shall supply representative samples of:*

- *The drug products proposed for marketing*
- *The drug substance or components used in the manufacturing of the drug products*
- *Reference standards*

VIII. ANDAs — WHAT SHOULD YOU INCLUDE IN YOUR ANDA?

This section of the guidance is based extensively on section 505(j) of the Act, and regulations in 21 CFR 314 subpart C. 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 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.

This section of the guidance discusses the content and format of an ANDA. If your drug is *the same as* an already approved NDA (e.g., FDG F 18 injection or sodium fluoride injection), you most likely will 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 separate attachments.

Before beginning to fulfill the submission requirements of the ANDA, determine whether your product is the same as the reference listed drug (RLD) (see Table 3). Some differences are permitted; they are discussed below.

Table 3: Product descriptions

FDG F 18 Injection	
Active ingredient	2-Deoxy-2[18F]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 - 40 mCi/mL at EOS (end of synthesis)*
Osmolality	Isotonic
pH	5.5 - 7.5
Route of administration	Intravenous

* There is an approved ANDA suitability petition for FDG F 18 injection that involves changes in strength, including mCi/mL, total activity and total drug content, from the reference listed drug (Docket No. 97P-0432/CP1).

Sodium Fluoride F 18 Injection

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

Although drugs approved in ANDAs are generally the same as the RLD, there are certain changes that are permitted. The differences that may be permitted include

- a different dosage form
- a difference in strength
- a different route of administration.

For example, a change in the specific concentration (in mCi/mL), total drug content and/or in the amount of active ingredient is considered a change of strength.

If you wish to submit an ANDA with changes in any of these, *you must submit an ANDA suitability petition* and obtain permission to file an ANDA with such a change (see section VI.E). You will have to demonstrate in the suitability petition that the difference has no effect on the safety and effectiveness of the drug product. Suitability petitions must be submitted to the FDA and approved *before* you can submit your ANDA.[28] The Agency usually acts on an ANDA suitability petition in 90 days. However, competing priorities can delay this to up to 6 months.

Remember, if your proposed drug differs from the RLD and you decide you do not wish to submit an ANDA suitability petition, you have the option of submitting a 505(b)(2) NDA. If you have questions, contact the Office of Generic Drugs at 301-827-5845.

[28] Section 505(j)(2)(C)(I) of the Act There is an approved ANDA suitability petition for FDG F 18 injection (Docket No. 97P-0432/CP1).

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. This guidance and the already approved NDAs for these PET drugs form the basis for your ANDA submission for FDG F 18 injection or sodium fluoride F 18 injection. Once an NDA has been approved for ammonia N 13 injection, applicants will be able to submit ANDAs for this PET drug using the approved product as the RLD.

When an ANDA is submitted to the FDA, 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.

Your completed application should be sent to:[29]

Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Rm. 150
7500 Standish Place
Rockville, MD 20855

An ANDA usually contains *a cover letter*, a completed and *signed application form* (Form FDA 356h), and a number of *individual items* based on the regulations.

A. Cover Letter

The application should include a signed and dated cover letter with a clear, brief introductory statement. The cover letter should be on the applicant's letterhead stationery, if possible. The cover letter should contain the following information:

- ***Purpose of the application*** (to obtain approval of an ANDA to market (*name of drug*) for (*indication*) as stated above)

- ***Type of submission*** (your application will probably be an Original Application)

- ***Name, title, signature, and address of the applicant***. The *applicant* is any person who submits an NDA or ANDA to obtain FDA approval to market a drug. It also includes any person who owns an approved NDA or ANDA. Usually, the name, title, signature, and address of the applicant belong to a *responsible official*. Typically, commercial manufacturers

[29] Some data in an ANDA can be submitted electronically. See discussion of electronic submissions in section VI.

have an employee in the regulatory affairs department submit an application on their behalf. This person serves as the *responsible official.*

- ***Establishment and proprietary name (if any)*** for the proposed drug product. The established name is often referred to as the *generic name* of a drug product. For the PET drug products in this section, the established names are (1) fludeoxyglucose F 18 injection and (2) sodium fluoride F 18 injection. It is not necessary to provide a proprietary or trade name for these PET drug products in your application.

- ***Number of volumes submitted.*** Depending on the size of your application, you may want to divide the application into separate volumes for easier handling.

B. Application Form

The application is Form FDA 356h.[30] 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 information, (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 a particular section does not apply, please write "NA" (not applicable).

2. Product description

The descriptions in Table 4 should be used in completing this section for these two PET drugs:

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

Table 4: Example of product descriptions for use in PET drug application

Established Name:	Fludeoxyglucose F 18 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) reference time
Route of Administration:	Intravenous

3. Application information

This section asks for information about the *type of application* you are submitting (NDA or ANDA).[31]

- Check the appropriate application type in the first box (ANDA).
- 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*). The product designated with the symbol (+) is the drug product selected by the FDA as the reference standard for conducting bioequivalence testing.

  For FDG F 18 injection, the RLD should be listed as follows:

  NDA 20-306, Fludeoxyglucose F 18 Injection, held by Methodist Medical Center of Illinois.

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

[31] BLA (for biological drug products being submitted to the Center for Biologics Evaluation and Research) does not apply to these PET drugs.

For sodium fluoride F 18 injection, the RLD should be listed as follows:

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

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

Currently, the Agency cannot accept ANDAs for N 13 ammonia because there is no approved NDA for N 13 ammonia at this time.

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

4. Establishment information

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

In the next part, Cross References, you may want to reference other applications in your ANDA. 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.

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 C, below. The items required for an ANDA differ from those on page 2 of Form FDA 356h. Please use the list presented in section C as the proper list of individual items to be submitted.

6. 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 is developing current good manufacturing practice (CGMP) requirements for PET drugs. In the future, Form FDA 356h will be changed to reflect the PET drug industry's need to comply with PET current good manufacturing practice regulations. Until then, in addition to the certification statement, provide the following signed 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.*

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.

C. 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 the 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 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)
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. Sample statement
9. Financial disclosure
10. Debarment certification
11. Field copy certification
12. 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, see the sample formats for the chemistry sections in the attachments. We have prepared sample formats for chemistry sections for the PET drug products addressed in this section.

1. Table of contents

All ANDAs should include a table of contents following Form FDA 356h. See also FDA's guidance for industry, O*rganization of an ANDA* (February 1999), which contains a model for an ANDA table of contents.

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, 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 (reference listed drug)

Cite the RLD. In ANDAs, a comparison between the generic drug and the RLD is the required basis for the submission. List the RLD you will be using in the application based on the following:

For FDG F 18 injection, the RLD should be listed as follows:

NDA 20-306, Fludeoxyglucose F 18 Injection, held by Methodist Medical Center of Illinois.

Note: If the FDA approves other NDAs for FDG 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 follows:

NDA 17-042, (18 F) as Fluoride Ion in Saline Solution, held by Nycomed-Amersham, Inc.

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

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*.[32]

Currently, there are no patents listed in the *Orange Book* for the approved PET drugs, fludeoxyglucose F 18 injection and sodium fluoride F 18 injection. Because there are no listed patents, you must provide a *no relevant patents certification* in your ANDA.

Here is an example of a no relevant patents certification statement that you can use for FDG F 18 injection and sodium fluoride F 18 injection.

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.[33] 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.[34]

[32] Additional information about patent certifications can be found in 21 CFR 314.94(a)(12).
[33] 21 CFR 314.108(b)

[34] 21 CFR 314.94(a)(ii)

Here is an example of a no exclusivity statement you can use for FDG F 18 injection and sodium fluoride injection in your ANDA.

> According to the publication *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)(4)(D) of the Act (21 U.S.C. 355(j)(4)(D)).

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

There are a limited number of ways in which the *inactive ingredients* in a generic parenteral (injectable) drug, such as a PET drug, can differ from the RLD. The formulation for generic injectable drug products is allowed to differ from that of the RLD only in preservative, buffer, and/or antioxidant.[35] The differences are *not allowed to affect* the safety or effectiveness of the generic drug.

Following a brief discussion of each, an example statement is provided in the box at the end of this section along with a table showing a comparison of the proposed generic with the RLD for both FDG F 18 injection and sodium fluoride F 18 injection (Table 5).

- Conditions of use

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 sample statements below).

- Active and inactive ingredients

[35] 21 CFR 314.94(a)(9)(ii) and (iii)

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 sample statements below).

If your formulation contains a different preservative, buffer, and/or antioxidant from that of the RLD, the ingredients that are different (inactive ingredients) need to have been approved previously in another drug product given by the same route of administration. The use of such an approved inactive ingredient should not exceed the ranges in the previously approved product. To see if such an inactive ingredient has been approved previously in a drug product given by the same route of administration, see FDA's *Inactive Ingredient Guide*.[36]

If the inactive ingredients in a generic injectable drug product differ from the RLD in ways other than in preservative, buffer, and/or antioxidant, an ANDA should not be submitted. In this case, a 505(b)(2) NDA would be appropriate.

- Route of administration, dosage form, and strength

Please 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 sample statements below).[37]

Here is a sample 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.

> 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 the RLD.

If differences exist between your proposed drug and the RLD and you have obtained approval of an ANDA suitability petition (see discussion at the beginning of the section on ANDAs), these differences should be explained and a *copy of the suitability petition approval letter* should be included.

Tables 5 and 6 compare the proposed drug with the RLD for FDG F 18 injection and sodium fluoride F 18 injection, respectively. You can adapt this table and insert it into your application under Comparison of RLD and generic drug.

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[36] The FDA's *Inactive Ingredient Guide* is available through a Freedom of Information (FOI) request to the FDA.

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

Table 5: Comparison of proposed generic FDG F 18 injection with the RLD

	Generic Drug	**RLD**
Conditions of use:	Fludeoxyglucose F 18 injection is indicated in PET for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.	Fludeoxyglucose F 18 injection is indicated in PET for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.
Active ingredient:	2-Deoxy-2[18F]fluoro-D-glucose	2-Deoxy-2[18F]fluoro-D-glucose
Route of administration:	Intravenous	Intravenous
Dosage form:	Injection	Injection
Strength:	4 – 40 mCi/mL (EOS*)	4 – 40 mCi/mL (EOS*)[*]

* End of synthesis

Table 6: Comparison of proposed generic sodium fluoride F 18 injection with the RLD

	Generic Product	**RLD**
Conditions of use:	Sodium fluoride F 18 injection is used as a bone imaging agent to define areas of altered osteogenic activity.	Sodium fluoride F 18 injection is used as a bone imaging agent to define areas of altered osteogenic activity.
Active ingredient:	Sodium fluoride F 18	Sodium fluoride F 18
Route of administration:	Intravenous (primary) oral (alternative)	Intravenous (primary) oral (alternative)
Dosage form:	Injection	Injection
Strength:	2.0 mCi/mL at calibration time (4.2-0.22 mCi/mL)	2.0 mCi/mL at calibration time (4.2-0.22 mCi/mL)

5. Labeling

[*] There is an approved ANDA suitability petition for FDG F 18 injection that involves changes in strength, including mCi/mL, total activity and total drug content, from the reference listed drug (Docket No. 97P-0432/CP1).

You must submit four (4) copies of a draft product label and all labeling for the drug product. The term *product labeling* is a collective term that includes the package insert, vial labels, and carton labeling. Sample formats for draft product labeling for each PET drug can be found in the attachments. These sample formats comply with all of the requirements for product labeling and can be easily adapted as part of your application.

You will need to add appropriate information as indicated in the sample formats for the draft labeling. You need to include a side-by-side comparison of your package insert and container labels with the RLD with all differences annotated and explained. See the attachments for sample formats for labeling for FDG F 18 injection and sodium fluoride F 18 injection.

After the labeling review is complete, the labeling reviewer will ask you to submit 12 copies of the final printed labeling. You will be asked to submit the labeling as *an amendment* to the application. This usually occurs prior to the approval of the application.

6. Bioequivalence

If your injectable product contains the same active and inactive ingredients as the RLD in the same concentration, you do *not* have to provide an in vivo study that shows that the drug product is bioequivalent to the RLD.[38] You are then eligible for *a waiver* of the in vivo study. 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).*

This section of the application also should include a *side-by-side comparison* of the formulation of the proposed generic drug and the RLD.

Here are examples of side-by-side comparisons for each drug that you can adapt to your application.

[38] 21 CFR 314.94(a)(7); 21 CFR 320.22(b)(1)

Table 7: FDG F 18 injection: side-by-side comparison (applicant fills in missing information)

Description	RLD	Applicant's Proposed Drug Product
Active Ingredient: 2-Deoxy-2-[^{18}F]fluoro-D-glucose	4 mCi to 40 mCi/mL @ EOS*	_?_ mCi to _?_ mCi/mL @ EOS*
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

- End of Synthesis

Table 8: Sodium fluoride F 18 injection: side-by-side comparison (Applicant fills in missing information)

Description	RLD	Applicant's Proposed Drug Product
Active Ingredient: 2-Deoxy-2-[^{18}F]fluoro-D-glucose	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

7. Chemistry section

We have provided as separate attachments sample formats for chemistry sections for each of these PET drugs. You can use these sample formats to provide information and data regarding your manufacture of these PET drugs.

If questions arise, please contact the Division of Medical Imaging and Radiopharaceutical Drug Products at 301-827-7510.

8. Sample statement

At some time during the application process, the FDA may request that you provide representative samples. Generally, when the FDA asks for a representative sample, it is a sample of the drug product proposed for marketing, the drug substance or components used in the manufacturing of the drug product, or the reference standards. If the Agency makes such a request, it will state specifically what materials are requested, how to provide the representative sample, and any additional information that is needed. If you are asked to provide a sample of material, you must include a statement with the requested material.

Here is an example of a sample statement.

Upon request of the FDA, (Name of applicant*) shall supply representative samples of:*

- *The drug products proposed for marketing*
- *The drug substance or components used in the manufacturing of the drug products*
- *Reference standards*

9. Financial disclosure

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

No financial certification or disclosure statements by clinical investigators are required as part of the applications for FDG F 18 injection or sodium fluoride F 18 injection.

10. 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.[39]

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 ANDA applicants should include a nonconviction statement or, if necessary, they must include information about any convictions (of the company or affiliated persons) that could have led to debarment (felonies or misdemeanors related to the development or approval of any drug).[40]

If you or anyone else who is responsible for the development or submission of the ANDA have 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 occurred within 5

[39] Use of a debarred individual/firm may preclude the approval of the application.
[40] See 21 U.S.C. 335a(k).

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.

11. 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 *chemistry 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 Office of Compliance in the Center for Drug Evaluation and Research at 301-594-0054.

12. Other

- Letters of Authorization:

If you use an agent or consultant to act on your behalf, you need to include in the application letters of authorization that identify these agents or consultants. Any letter of authorization should be signed by the applicant and placed following the cover letter.

- User Fees

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

ATTACHMENTS
(available as separate documents)

The following sample formats are available as separate documents.

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

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

II. Sample formats for labeling

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

III. Sample formats for Form FDA 356h:

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

IV. Sample formats for user fee Form FDA 3397

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