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Guidance for Industry¹

PET Drug Applications — Content and Format for NDAs and ANDAs

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

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.

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.

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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

³As 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.

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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)

-
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>

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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.

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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 *NDA*s 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 *NDA*s 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.

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.

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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).

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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

- | |
|--|
| <ul style="list-style-type: none">• 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*.

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.

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- 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.

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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.

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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.

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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

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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*.

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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:

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).