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*.

---

[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:

---

[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.