

Draft — Not for Implementation

*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.

Draft — Not for Implementation

- 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).

Draft — Not for Implementation

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).

Draft — Not for Implementation

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.

Draft — Not for Implementation

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.

Draft — Not for Implementation

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

Draft — Not for Implementation

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

Draft — Not for Implementation

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, *Organization 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)

Draft — Not for Implementation

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)

Draft — Not for Implementation

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.

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).

Draft — Not for Implementation

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*	<u> ?</u> mCi to <u> ?</u> mCi/mL @ EOS*
Inactive Ingredients: Sodium chloride injection, USP (Sodium chloride in WFI)	9 mg/mL	<u> ?</u> 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)	<u> ?</u> mCi/mL @ calibration (<u> ?</u> - <u> ?</u> mCi/mL)
Inactive Ingredients: Sodium chloride injection, USP (Sodium chloride in WFI)	9 mg/mL	<u> ?</u> 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.

Draft — Not for Implementation

If questions arise, please contact the Division of Medical Imaging and Radiopharmaceutical 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

Draft — Not for Implementation

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).

Draft — Not for Implementation

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