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

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

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

B. Application Form

The application is Form FDA 356h.[30] This form should be completed and signed by the applicant, or the responsible official.

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

1. Applicant information

This section requests general information about the applicant: name, address, telephone number, and fax number. If a particular section does not apply, please write "NA" (not applicable).

2. Product description

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

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

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

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

3. Application information

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

- Check the appropriate application type in the first box (ANDA).
- Write "NA" in next box and go to the third box.
- In this box, you are asked to provide general information on the RLD. An ANDA must state the name of the RLD including its dosage form and strength as identified by the symbol (+) in the *Approved Drug Products With Therapeutic Equivalence Evaluations* (the *Orange Book*). The product designated with the symbol (+) is the drug product selected by the FDA as the reference standard for conducting bioequivalence testing.

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

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

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

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

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

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

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

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

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

4. Establishment information

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

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

5. The individual items based on the regulations

This is the longest, most detailed part of Form FDA 356h. The individual items in this section are discussed in detail in section C, below. The items required for an ANDA differ from those on page 2 of Form FDA 356h. Please use the list presented in section C as the proper list of individual items to be submitted.

6. Certification

This section is at the end of Form FDA 356h following the individual items. It provides your certification to the FDA that the information you are providing is true to the best of your knowledge. You also agree

to update specific parts of your application as needed and submit required safety reports. Finally, the Certification states that you agree to comply with all applicable laws and regulations.

- Current good manufacturing practices

As directed by section 121 of the Modernization Act, the FDA is developing current good manufacturing practice (CGMP) requirements for PET drugs. In the future, Form FDA 356h will be changed to reflect the PET drug industry's need to comply with PET current good manufacturing practice regulations. Until then, in addition to the certification statement, provide the following signed statement in your application:

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

7. Signature of responsible official

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

C. Individual Items in the Application

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

An ANDA contains the following individual items or sections:

1. Table of contents
2. Basis for ANDA submission (reference to listed drug)
3. Patent certification and exclusivity statement
4. Comparison of RLD and generic drug
   - Conditions of use
   - Active and inactive ingredients
   - Route of administration, dosage form, and strength
5. Bioequivalence information
6. Labeling

7. Chemistry, manufacturing, and controls information
8. Sample statement
9. Financial disclosure
10. Debarment certification
11. Field copy certification
12. Other

This list, which corresponds to the following discussion, identifies what should be included and can be used as a road map for organizing the application. In addition, see the sample formats for the chemistry sections in the attachments. We have prepared sample formats for chemistry sections for the PET drug products addressed in this section.

1. Table of contents

All ANDAs should include a table of contents following Form FDA 356h. See also FDA's guidance for industry, *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)

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

> According to the publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (*Orange Book*), the reference listed drug is not entitled to a period of marketing exclusivity under Section 505(j)(4)(D) of the Act (21 U.S.C. 355(j)(4)(D)).

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

4. Comparison of RLD to generic drug

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

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

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

- Conditions of use

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

- Active and inactive ingredients

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

Provide a statement that the active ingredient in the proposed drug product is the same as the active ingredient in the RLD. In the statement, indicate that you have provided the necessary information in the Labeling section of the application (see sample statements below).

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

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

- Route of administration, dosage form, and strength

Please provide a statement that the route of administration, dosage form, and strength of the proposed drug product are the same as those of the RLD (see sample statements below).[37]

Here is a sample statement you can use if your product is the same as the RLD in active ingredient, conditions of use, route of administration, dosage form, and strength.

> The conditions of use prescribed, recommended, or suggested in the labeling proposed for the generic drug have been previously approved for the RLD.
>
> The active ingredient, route of administration, dosage form, and strength are the same as the RLD.

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

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

---

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

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

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

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

* End of synthesis

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

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

5. Labeling

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

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

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

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

6. *Bioequivalence*

If your injectable product contains the same active and inactive ingredients as the RLD in the same concentration, you do *not* have to provide an in vivo study that shows that the drug product is bioequivalent to the RLD.[38] You are then eligible for *a waiver* of the in vivo study. In this case, bioequivalence will be established based on other data in the application. You should request a waiver using the following language:

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

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

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

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

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

Description	RLD	Applicant's Proposed Drug Product
Active Ingredient: 2-Deoxy-2-[^{18}F]fluoro-D-glucose	4 mCi to 40 mCi/mL @ EOS*	_?_ mCi to _?_ mCi/mL @ EOS*
Inactive Ingredients: Sodium chloride injection, USP (Sodium chloride in WFI)	9 mg/mL	_?_ mg/mL
Specific Activity	No carrier added	?
Dosage form	Injection	Injection
Route of Administration	Intravenous	Intravenous

- End of Synthesis

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

Description	RLD	Applicant's Proposed Drug Product
Active Ingredient: 2-Deoxy-2-[^{18}F]fluoro-D-glucose	2 mCi / mL @ calibration (4.22 – 0.22 mCi / mL)	_?_ mCi/mL @ calibration (? - ? mCi/mL)
Inactive Ingredients: Sodium chloride injection, USP (Sodium chloride in WFI)	9 mg/mL	_?_ mg/mL
Specific Activity	No carrier added	?
Dosage form	Injection	Injection
Route of Administration	Intravenous	Intravenous

7. Chemistry section

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

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

8. Sample statement

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

Here is an example of a sample statement.

> *Upon request of the FDA,* (Name of applicant*) shall supply representative samples of:*
>
> - *The drug products proposed for marketing*
> - *The drug substance or components used in the manufacturing of the drug products*
> - *Reference standards*

9. Financial disclosure

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

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

10. Debarment certification

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

- Debarment certification

As of June 1, 1992, any ANDA must include certification that the applicant did not and will not use the services (in any capacity) of any person debarred under section 306(a) or (b) of the Act in connection with the submission of their application.[39]

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

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

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

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

- Convictions

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

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

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

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

If you or an affiliated person responsible for the development or submission of your application has a conviction(s) of a relevant offense that could lead to debarment and that conviction occurred within 5

---

[39] Use of a debarred individual/firm may preclude the approval of the application.

[40] See 21 U.S.C. 335a(k).

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

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

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

11. Field copy certification

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

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

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

If questions arise regarding the field copy, please contact the Office of Compliance in the Center for Drug Evaluation and Research at 301-594-0054.

12. Other

- Letters of Authorization:

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

- User Fees

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

ATTACHMENTS
(available as separate documents)

The following sample formats are available as separate documents.

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

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

II. Sample formats for labeling

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

III. Sample formats for Form FDA 356h:

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

IV. Sample formats for user fee Form FDA 3397

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

目 次

産業に向けたガイダンス[1]

PET 医薬品の申請 ---- NDA および ANDA の内容と形式

フルデオキシグルコース F 18 注射薬
アンモニア N 13 注射薬
フッ化ナトリウム F 18 注射薬

I. 緒言

このガイダンスは、陽電子(ポジトロン)放出断層撮影(PET)画像法に使用されるフルデオキシグルコース(FDG)F 18 注射薬、アンモニア N 13 注射薬、およびフッ化ナトリウム F 18 注射薬に関する新薬認可申請(NDA)または新薬認可簡易申請(ANDA)の作成について、申請を助けることを目的とする。NDA または ANDA の FDA 承認によって、Federal Food, Drug, and Cosmetic Act (連邦食品医薬品化粧品法; "Act" 」)[2]の要求事項に従って臨床用としてこれらの PET 医薬品を市場化することが可能になる。

このガイダンスには、(1) 簡単な背景情報、(2) NDA または ANDA の提出の決定を助ける情報、(3) NDA および ANDA に必要な内容と形式の完全な説明、および、(4) 申請書にコピーまたはカットアンドペーストして使用できる、ボックスで囲まれた本文が含まれている。内容と形式のセクションでは、これらの PET 医薬製品に関する NDA または ANDA の提出に必要なすべての情報を提供する。最後に、当局は、FDG F 18 注射薬、アンモニア N 13 注射薬、およびフッ化ナトリウム F 18 注射薬に関する内容およびフォーマットと、ラベリングの提案について、サンプルフォーマットを開発した。サンプルの申請およびユーザー料金カバーシートも提供している。付録はガイダンスに含まれず、別途提供される。

当局は、申請書作成のための時間、労力および資源の不要な消耗を避けるため、申請者が本ガイダンスに記載される指示に従うことを推奨する。

---

[1] このガイダンスは、Food and Drug Administration(食品医療局)の Center for Drug Evaluation and Research (医療品評価研究センター: CDER)の PET 運営委員会で作成された。本書は、一定のポジトロン放出断層撮影(PET)医薬製品の NDA および ANDA の内容と形式に関する "Agency" の現在の見解を表す。本ガイダンスは、特定の人物に関する権利を創出または授与するものではなく、FDA または公衆を拘束するものでもない。適用法令、規制、またはその両者の要求事項を満たすならば、代替のアプローチを使用することができる。

[2] 505(b)(2)の申請を含め、NDA は、"Act" のセクション 505(b)に基づいて提出される。"Act" のセクション 505(j)は

ANDA に適用される。
このガイダンスは、505(b)(2)の NDA または ANDA による提出内容について非常に詳細に説明しているので、特にセクション VII および VIII で広範な必須事項を表す表現を含むという点で、ほとんどのガイダンスとは異なっている。この必須事項の表現は、FDA 規制によって一定情報の提出が要求されるときに使用される。通常、他の文書では、必須事項の表現にはそれに関連する引用が伴うが、ここでは、ガイダンスをユーザーにとってより親しみやすいものにし、わずらわしさを和らげるため、要求事項に伴う各規制の引用は省略されている。

II. なぜ FDA が PET 医薬品を規制するのか

1997 年 11 月 21 日に、クリントン大統領は Food and Drug Administration Modernization Act of 1997(1997 年食品医療局近代化法; Pub.L.105-115; "Modernization Act")に署名し、法制化した。"Modernization Act" のセクション 121(c)は、FDA が PET 医薬品を規制することを指令している。セクション 121 は、以下を含めて、特定の時間枠内に FDA が実施すべき数多くのタスクを明らかにしている。

- FDA は、PET 医薬品の承認と、それらの医薬品に関する現行の医薬品製造規制(CGMP)の要求事項の承認に関する適切な手順を開発しなければならない。
- FDA は、これらの手順と要求事項を決定する過程において、患者擁護グループ、専門家団体、製造業者、および PET 医薬品の製造または使用の被認可者と協議を行う。
- FDA は、制定の日以後 4 年間、または PET 医薬品の特殊な承認手順と CGMP 要求事項を FDA が採択する日から 2 年後の、いずれか長い方の期間、"Act" に記載されるように粗悪化されていない混合 PET 医薬品に関して NDA または ANDA の提出を要求することはできない。このような申請の自発的な提出と FDA によるレビューは禁止されない。

III. FDA は新しい要求事項を満たすために何をしてきたか

FDA は、1997 年 11 月以来、"Modernization Act" のセクション 121 の実施を進めている。"Agency" は、PET 医薬品の承認手順および CGMP の要求事項に関する FDA 提案を協議するために、産業界の組織である Institute for Clinical PET(臨床 PET 協会; "ICP")のさまざまな代表者およびその他の関係者と、数回の公的会議を実施している。一定の PET 医薬品が長年の間臨床的に使用されているため、FDA は出版物について独自のレビューの実施を決定した。[3] FDA の目標は、広範に使用されている PET 医薬品の一定の表示に関して、安全性と有効性を評価し、PET 薬品産業のためにこれらの製品に関する申請提出の過程を容易にすることであった。

---

[3] 産業向け FDA ガイダンス、"Providing Clinical Evidence of Availability for Human Drugs and Biological Products (人間の医薬品および生態学的製品に関する利用可能性の臨床学的証拠の提供(1998 年 5 月))に記載されるように、FDA は、一定の状況において、"Act"のセクション 505 に基づく新薬製品の承認を裏づけするために、出版物のみに依存することができる。

FDAは、腫瘍学および心筋生存能力査定用のFDG F 18注射薬と、心筋血流査定用のアンモニアN 13注射薬を含めて、以前に承認を拒否された表示に関して、いくつかの一般に使用されているPET医薬製品について文献を再調査し、安全性と有効性の研究を評価した。"Agency"は、公的な会議において、ICPおよびその他の関係者と、これらの表示に関して、これらの医薬品の安全性および有効性に関する予備的な所見について協議した。1999年の6月28日から29日にかけて、"Agency"は、Medical Imaging Drugs Advisory Committee（医療画像法医薬品諮問委員会；"Advisory Committee"）にその所見を提示した。"Advisory Committee"は、FDAによって提案される表示の表現形式に多少の改正を推奨はしたが、FDG F 18注射薬とアンモニアN 13注射薬は、これらの表示に関して安全かつ有効であるとみなすことができるという結論にいたった。

IV. FDAの所見とは何か

FDAは、文献のレビューおよび所見と、"Advisory Committee"の推奨に基づいて、一定の表示に関するFDG F 18注射薬とアンモニアN 13注射薬に関するNDAおよびANDAの承認に関する規準を開発した(下記リスト参照)。PET医薬品と表示に関してすでに承認されたNDAについての"Agency"の所見は、癲癇発作の病巣に関するFDG F 18注射薬と骨の画像法表示に関するフッ化ナトリウムF 18注射薬の承認に対する規準である(以下のリスト中のアスタリスクの付けられた表示参照)*。

2000年3月のFederal Register(連邦官報)の告示(PETの安全性と有効性告示)[4]において、FDAは一定の表示に関する一定のPET医薬品の安全性と有効性について所見を発表した。「PETの安全性と有効性告示」で、以下記述される表示について、以下のPET医薬品に関して提出できる申請の様式を説明している。

フルデオキシグルコースF 18注射薬（FDG F 18）

1. フルデオキシグルコースF 18注射薬は、他のテストの様式的な属性によって発見された、既知のまたは疑わしい異常を持つ患者、または既存の癌の診断を持つ患者の、悪性腫瘍の評価を助けるため、グルコース代謝異常の査定用に、ポジトロン放出断層撮影(PET)画像法で表示される。
2. フルデオキシグルコースF 18注射薬は、残留グルコース代謝と心臓収縮機能の逆転ロスを持つ左心室心筋の表示のために、心筋灌流画像法と併せて使用されるとき、冠状動脈疾患と左心室機能障害を持つ患者について、ポジトロン放出断層撮影(PET)画像法で表示される。

*アスタリスクの付けられた表示は、以前のPET NDAで承認されている。

[4] Federal Register、2000年3月____、Volume 65、____ページ。次のFDAのPETインターネットページも参照のこと。
http://www.fda.gov/cder/regulatory/pet/default.htm