1992 年 6 月 1 日現在で、ANDA は、申請者が、申請の提出に関連して、"Act"のセクション 306(a)または(b)に基づいて除外される人物のサービス(資格を問わず)を使用しなかった、または今後使用しないという証明書を含まなければならない。[39]

除外とは、医薬品の開発または承認に関連する重罪または軽罪の有罪が決定された個人または会社が、申請者または製造業者に一定のサービスを提供するのを禁止するために FDA によって使用される管理手順である。通常、除外される者は、医薬品申請の提出に関連する不正手段の有罪が決定された個人または会社である。

除外証明書は申請者による自己査定である。申請者に必要なのは、除外と、除外に至る犯罪の有罪決定を証明書に含めることだけである。

次に、NDA で使用できる除外証明書の例を示す。

私、(申請者の氏名)は、私または我々が、この申請に関連して、Federal Food, Drug, and Cosmetic Act のセクション 306 に基づいて除外される人物の、いかなる資格でのサービスも使用しなかったことを、そして使用しないことを証明する。

o　有罪の決定

すべての ANDA 申請者は、無罪の決定ステートメントを含めなければならず、または、必要に応じて、除外に至る可能性のあった(会社または系列下の人物の)有罪の決定に関する情報を含めなければならない(医薬品の開発または承認に関する重罪または軽罪)。[40]

開発者または ANDA の開発または提出に責任のある者が、過去 5 年以内に関連犯罪の有罪が決定されていない場合、その趣旨の簡単なステートメントを提出しなければならない。

申請者が使用できる無罪ステートメントの例を以下に示す。

(申請者の名称)は、本申請に関連して過去 5 年以内に関連犯罪の有罪が決定された者の、いかなる資格でのサービスを使用しておらず、使用しない。

申請者または申請者の申請の開発または提出に責任のある者が、除外に至る可能性があり、かつ、申請日の前の 5 年以内に関連犯罪の有罪決定がなされている場合、申請者はこれらの有罪決定のリストを含めなければならない。有罪決定のリストは以下の情報を含まなければならない。

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[39] 除外された個人または企業を使用した場合は、申請の承認が排除される。

[40] 21 U.S.C. 335a(k)参照。

- o 有罪が決定された人物または会社の名称
- o 関連する連邦または州の法令のセクションの表題
- o 有罪決定の日付
- o 判決の下された日付
- o 判決を記録する裁判所
- o 知られている場合は訴訟番号
- o 犯罪の簡単な説明

さらに、申請者は、申請の開発における各有罪決定者の役割を説明しなければならない。除外証明書と有罪決定情報は、申請者の責任ある役員が、または申請に署名する責任者が署名しなければならない。

11. フィールドコピー証明書

ANDA のフィールドコピーは、PET センターによる承認前調査の間に FDA フィールド調査員が使用する。フィールドコピーは、化学のセクション、申請フォーム、および概要を含まなければならない。申請者は、それが申請のレビュ用一コピーに含まれる情報の正確なコピーであることを証明しなければならない。

次に申請者が使用できるフィールドコピー証明書の例を示す。

(申請者の氏名)は、フィールドコピーが、21 CFR 314.50(l)(3)に記載され、申請の記録保管用コピーおよびレビュー用コピーに含まれる申請書の技術セクションの真実のコピーであることを証明する。

フィールドコピーに関して疑問が発生した場合は、Center for Drug Evaluation and Research の Office of Compliance、(301)594-0054 に連絡のこと。

12. その他

o 承諾書

申請者が代理として代理人またはコンサルタントを使用する場合、これらの代理人またはコンサルタントを明示する承諾書を申請に含める必要がある。申請書は申請者が署名し、カバーレターの次に入れなければならない。

o 使用料金

505(j) 申請には料金は適用されない。ユーザー料金カバーシートに記入する必要はない。

Fludeoxyglucose F 18 Injection
CMC Sections

Fludeoxyglucose F 18 Injection

1. DRUG PRODUCT COMPONENTS AND QUANTITATIVE COMPOSITION

Component	Composition/mL	Composition/batch
Drug Substance 2-Deoxy-2[^{18}F]fluoro-D-glucose	_____ to _____ mCi @EOS[1] (____ to _____ MBq @ EOS)	____ to _____ mCi@EOS[1] (____ to ____ MBq @ EOS)
Other ingredient(s)[2] 1. _____ (e.g., Sodium chloride injection, USP) 2. _____	_____ (e.g., 1 mL) _____	_____mL _____

1. EOS = End of synthesis calibration time.
2. Provide all other ingredients used in drug product. Examples of other ingredients include diluents, buffers, stabilizers, preservatives.

2. CONTROLS FOR COMPONENTS / RAW MATERIALS

A. **ORGANIC SUBSTRATE** (Starting material if purchased from a qualified supplier. If the component is prepared in-house or obtained in any other manner, additional information concerning its manufacture and controls should be included)

Provide the name [e.g., 1,3,4,6-Tetra-O-acetyl-2-O-trifluoromethanesulfonyl-□-D-mannopyranose (mannose triflate)] and following information for the organic substrate used:

1.	Name of component	
2.	Name and address of supplier	
3.	Is this component further purified on site?	_____ Yes _____ No. If yes, method of purification is provided in attachment _____, page_____.
4.	Specifications - Provide tests to control identity, purity and quality, test procedure used, and acceptance criteria for each test	TEST — ACCEPTANCE CRITERION Appearance _____ Specific identity _____ (e.g., IR, NMR) Purity _____ (e.g., chromatography) Melting point _____

		Optical rotation _____ Attachment _____, Page _____
5.	Representative certificate of analysis (COA) from supplier	Copy of representative certificate of analysis is provided in attachment _____, page_____.
6.	Identity test performed to confirm structure to release the lot for production use	TEST PROCEDURE ACCEPTANCE CRITERION _____ _____ _____ The standard test procedures (STP) or standard operating procedure (SOP) is provided in attachment _____, page_____.
7.	Storage conditions	1. Container/closure _____ 2. Stored at _____ 3. The material is stable for _____ months/year, when stored in above container/closure under described storage conditions: attachment _____, page _____.

B. TARGET MATERIAL (Starting material)/RADIOACTIVE FLUORIDE REAGENT (Key intermediate)

We will produce radioactive fluoride reagent on site at the PET drug production facility? _____Yes ____No.

If yes, provide full details in section (i) below; otherwise proceed to section (ii).

(i) The following target material will be used for the production of radioactive fluoride reagent:

1.	Name of the target material	[^{18}O] Water
2.	Name and address of the target material manufacturer	
3.	Specifications [Tests, procedures, and acceptance criteria to control identity, purity, and quality should be proposed]	TEST ACCEPTANCE CRITERION Attachment _____, Page _____.
4.	Identity test performed to release each lot for production use	TEST PROCEDURE ACCEPTANCE CRITERION _____ _____ _____ The STP (or SOP) is provided in attachment _____, page_____.
5.	Certificate of analysis (COA)	Copy of representative supplier's certificate of analysis

		is provided in attachment _____, page_____.
6.	Is the target material recycled?	_____ Yes _____ No. If yes, its reprocessing procedures are described in attachment _____, page_____. Does the reprocessed material meet the acceptance criteria for the target material? ____ Yes _____No. [Note: If the recycled material does not meet the acceptance criteria for the target material, its use may not be acceptable]

We intend to use additional suppliers for this target material: _____Yes _____No.

If yes, for each additional supplier, the target material information specifically identified in items 1, 2, and 5 above is provided in attachment _____, page_____.

(ii) We will use the radioactive fluoride reagent, obtained from other sources, for the production of 2-deoxy-2[^{18}F]fluoro-D-glucose: _____Yes _____No.

If yes, provide the following information for each supplier of radioactive fluoride reagent:

1.	Name and composition of the fluoride reagent solution	
2.	Name and address of manufacturer	
3.	Method of preparation	☐ 1. The fluoride reagent is prepared using a ____MeV particle accelerator using $^{18}O(p, n)^{18}F$ reaction on $H_2{}^{18}O$. ☐ 2. The fluoride reagent is reactor produced. If fluoride is produced by methods described in 2, provide a description of the method of preparation, purification, and acceptance criteria that are appropriate for such production method. Information is provided in attachment _____, page_____.
4.	Test and acceptance criteria	TEST — PROCEDURE — ACCEPTANCE CRITERION Identity _____ _____ Purity _____ _____ Radioconcentration _____ _____ (if applicable) _____ _____ _____ Attachment _____, page _____.
5.	Provide procedure(s) used to	

	release each lot of the reagent for use in production	Attachment _____, page_____.
6.	Certificate of analysis	Copy of representative certificate of analysis is provided in attachment _____, page _____.

We intend to use additional suppliers for this fluoride reagent: _____Yes _____No.

If yes, for each additional supplier, the fluoride reagent information is provided in attachment _____, page_____.

C. OTHER INGREDIENTS

The following other ingredient(s) are used in the formulation of finished fludeoxyglucose F 18 injection.

Name	Purpose	Name and address of manufacturer	Specifications, representative COA and acceptance criteria for each lot
			Attachment ___, page ____.
			Attachment ___, page ____.

Note: COA need not be provided if ingredient is an approved drug product. If additional ingredients are used, they should be listed and information provided in attachment _____, page _____.

D. REAGENTS, SOLVENTS, GASES, PURIFICATION COLUMNS, AND OTHER AUXILIARY MATERIALS

Provide following information for each reagent, solvent, gas, purification column, and other auxiliary material that is used in the production of fludeoxyglucose F 18 injection:

	Name	Name and address of the supplier	Quality grade (e.g., ACS, USP, etc.) or specifications, representative COA and acceptance criteria for each lot
1			Attachment _____, page ____.
2			Attachment _____, page ____.
3			Attachment _____, page ____.

4			Attachment _____, page ____.
5			Attachment _____, page ____.
6			Attachment _____, page ____.
7			Attachment _____, page ____.

Note: Information on additional other ingredients is provided in attachment _____, page _____.

3. REFERENCE STANDARDS

The following reference standards are used in the quality control methods of fludeoxyglucose F18 injection:

[Note: Following are presented as an example. Reference standards appropriate for the synthesis should be included here. If a reference standard is obtained from USP, it should be so stated. If a reference standard is not obtained from USP, data to support that the reference standard lot has the desired structure must be submitted in the indicated attachment. Purity of the reference standard lot should be provided.]

	Name of reference standard	Name and address of the supplier	Specifications, representative COA and acceptance criteria for each lot
1	2-Fluoro-2-deoxy-D-glucose		Attachment __, page____
2	2-Chloro-2-deoxy-D-glucose		Attachment___, page____
3	Kryptofix, 222 (4,7,13,16,21,24-hexaoxa-1,10diazabicyclo[8.8.8]hexacosane)		Attachment___, page____

4. MANUFACTURING AND TESTING FACILITIES

Name of PET drug production facility: _____

Address: _____

Name of contact person: _____
Phone number of contact person: _____

Additional manufacturing and/or testing facilities (if any), including their function, are listed in attachment _____, page ____.

5. MANUFACTURE OF DRUG SUBSTANCE

A. BATCH FORMULA: The following components and their quantities are used in the production of each batch of 2-deoxy-2[^{18}F]fluoro-D-glucose:

Provide below the name of each component used in the production of 2-deoxy-2[^{18}F]fluoro-D-glucose, whether or not it appears in the final product; its function; and the amount (mass or volume) used in each batch (include all reactants, solutions, solvents, and reagents used in the chemical synthesis and purification operation).

Name of component	Component's function	Amount used
[Example: 1,3,4,6-Tetra-O-acetyl-2-O-trifluoro methanesulfonyl-□-D-mannopyranose]		_____ mg ± __mg
[^{18}F]Fluoride reagent		_____mCi to _____mCi

NOTE: Upon scale-up, only the mCi amount of radioactive [^{18}F]fluoride reagent is changed. The other components and their amounts remain as stated in the batch formula.

B. PRODUCTION OF RADIONUCLIDE

We will produce radioactive fluoride reagent only on site at the PET drug production facility?____Yes___No.

NOTE: If the radioactive fluoride reagent is obtained from outside sources, the following information (i, ii, & iii), and information for the recycling of the target material should be provided on the supplier's signed and dated letterhead.

(i) Particle Accelerator (e.g., cyclotron) Used

The following particle accelerator is used for the production of [^{18}F]fluoride radionuclide:

MAKE : _____
MODEL: _____

Information concerning additional particle accelerators is provided in attachment _____, page _____.

(ii) Operating Parameters

- During irradiation a beam current of _____ □A ± _____ □A is used.
- Irradiation times of _____ minutes to _____ minutes are used.
- We *use/do not use* high-pressure targets. When high-pressure targets are used, irradiations are performed under _____ *psi* pressure.

(iii) Specifications for Target Body

- Volume of the target _____ □l or ml.
- The target body used in our production operation is composed of _____.
- The target windows used in our targets are _____ (state thickness) and are composed of _____
- The schedule for the replacement of target windows is _____.
- The acceptance criteria for the target body and the target windows (that come in contact with target material) are provided in attachment _____, page _____.

If multiple target bodies of different types are used, the above information concerning each is provided in attachment _____, page _____.

C. SYNTHESIS AND PURIFICATION OF THE DRUG SUBSTANCE

(i) Description of Radiochemical Synthesis and Purification Equipment

Descriptions of the radiochemical synthesis and purification equipment, including components, their acceptance criteria, and a schematic flow diagram are provided in attachment _____, page _____.

We use the following synthesis and purification unit(s):

Make _____
Model _____

If more than one unit is used, and if units are different, provide information for each in attachment _____, page _____.

(ii) Description of Radiochemical Synthesis and Purification Operation

A step-wise description of the synthesis and purification procedure, including the amount of each reactant, reagent, solvent used, and acceptable radiochemical yields obtained, is provided in attachment _____, page _____.

(iii) In-Process Controls

All controls that are necessary to assure reproducible production of the stated drug should be

described. The following are examples of the in-process parameters that should be controlled in the synthesis and purification procedure:

- Drying of radioactive fluoride ions during the azeotropic evaporations.
  Number of azeotropic evaporations performed: _____.
  For evaporation, the vessel is heated between: _____°C to _____°C for _____minutes.

- Temperature and duration of reaction between radioactive fluoride ions and mannose triflate.

  The reaction vessel is heated between _____°C to _____°C for _____minutes.

- Temperature and duration of the hydrolysis reaction.
  The reaction vessel is heated between _____°C to _____°C for _____minutes.

- The amount of reactants, reagents, solvents, and solutions during each phase of synthesis and purification is controlled as described in master production and control records. _____ Yes.

- Flow rate of gas used for movement of materials within the synthesis and purification equipment.
  The flow rate used is _____.

- Total synthesis and purification time.
  The synthesis and purification operation takes a total of _____ minutes.

- Other parameters (provide any additional parameters that are controlled in your individual operation):
  Attachment _____, page _____.

  All in-process controls are monitored and documented in the master production and controls records:
  ___ Yes.

(iv) Post-Synthesis Procedures

Descriptions of procedures used to prepare the production equipment, including any cleaning and purging procedures, for a subsequent batch are provided in attachment _____, page _____.

6. MANUFACTURE OF DRUG PRODUCT

A. PRODUCTION OPERATION

The drug substance 2-deoxy-2[^{18}F]fluoro-D-glucose is not isolated. The synthesized, purified drug substance obtained from the synthesis and purification procedure is collected in the drug product vial. The specific procedures used in the formulation and preparation of our finished drug product are provided in attachment _____, page _____.

The master production and control records which provide the exact procedures used in the controlled production of and ensure full traceability of all components, materials, and equipment used for each batch of fludeoxyglucose F 18 injection, are provided in attachment _____, page _____.

B. REPROCESSING OF PET DRUG PRODUCT

☐ A manufactured PET drug product batch or lot will not be reprocessed.

☐ A manufactured PET drug product batch or lot may be reprocessed under the conditions (circumstances) specifically described in attachment _____, page _____.

The validated procedures (include SOP) used in reprocessing are described in attachment _____, page _____.

C. PACKAGING AND LABELING

The components used in the packaging of the drug product vial and the method of labeling are described in master production and control records on page _____ (attachment _____). The specifications and the acceptance criteria for the packaging component are provided in attachment _____, page _____. .

7. CONTAINER/CLOSURE

- We use a presterilized, presealed, pyrogen-free container/closure, consisting of USP Type I glass, gray butyl rubber stopper, and aluminum crimp seal, from an established commercial supplier._____Yes _____ No.

- If no, full information on the container/closure along with its sterilization procedures and sterility assurance is provided in attachment _____, page _____.

- If yes, the _____ ml container/closure, consisting of USP Type I glass, gray butyl stopper, and aluminum crimp seal, is obtained from the following manufacturer. The specifications and acceptance criteria for each lot of the container/closure are provided in attachment ____, page _____.

Container/Closure catalog # _____
Name and address of supplier _____
_____
_____
Drug master file number _____

A letter of authorization from the DMF holder, authorizing FDA to refer to the DMF in connection with our application, is provided in attachment _____, page _____.

8. CONTROLS FOR THE FINISHED DOSAGE FORM

A. SAMPLING PROCEDURES

Each batch of fludeoxyglucose F 18 injection will be produced for distribution:
- In a single multidose vial _____ .
- In multiple vials (single or multiple dose) _____. .

(i) If each batch is produced in a single vial, a description of the amount of volume that is withdrawn from the finished drug product container and how it is distributed among individual tests is provided in attachment _____, page _____.

(ii) If each batch is produced in multiple vials, a description of sampling techniques that assure that the test sample is representative of the entire batch is provided in attachment _____, page _____.

B. REGULATORY SPECIFICATIONS, PROCEDURES, AND TESTING SCHEDULES

Each batch of the fludeoxyglucose F 18 injection will meet the following specifications during its entire shelf life when tested according to the standard test procedures (STPs) described in this application.

[Note: The following tests are related to a commonly used production method. In the event that the production method does not use a component listed below or uses an alternate method of production or produces additional impurities, appropriate tests, acceptance criteria, procedures, and a testing schedule that is more appropriate for such production should be proposed.]

TEST	ACCEPTANCE CRITERIA	PROCEDURES	TESTING SCHEDULE
Appearance	Colorless and free from particulate matter when observed visually behind leaded glass	Visual observation under adequate light STP#_____	Test completed prior to release of drug product
Radionuclidic identity	The measured half-life is between 105.0 – 115.0 minutes	Measurement of radioactivity decay of the sample over a 10 minutes STP#_____	Test completed prior to release of drug product
Radiochemical identity	The Rf of 2-deoxy-2[^{18}F]fluoro-D-glucose corresponds (+/-10%) to the Rf (about 0.4) of 2-deoxy-2-fluoro-D-glucose reference standard, when both are chromatographed together side by side on the same TLC	TLC, activated silica gel plate developed in 95:5 / acetonitrile : water (TLC scanned in a radio-chromatographic scanner) STP#_____	Test completed prior to release of drug product
Radionuclidic purity	State limit	Gamma spectroscopy of decayed sample STP#_____	State schedule
Radiochemical purity	NLT[1] 90.0% 2-deoxy-2[^{18}F]fluoro-D-glucose	TLC, activated silica gel plate developed in 95:5/ acetonitrile : water STP#_____	Test completed prior to release of drug product
Radiochemical	NMT[2] 4.0 % fluoride F 18	Provide procedure	Test completed

impurities	(free)	STP# _____	prior to release of drug product
Assay (radioactivity concentration)	____mCi to ____ mCi / mL @ EOS (This should be same as stated strength of drug product)	USP STP# _____	Test completed prior to release of drug product
Specific activity	No carrier added 2-deoxy-2[^{18}F]fluoro-D-glucose	None - prepared by no carrier method of synthesis	No testing performed
PH	Specify limits	pH paper with pH reference standards STP# _____	Test completed prior to release of drug product
Kryptofix 222 (if used in synthesis)	The size and intensity of the spot in test sample, that corresponds to the 50□g/ml kryptofix 222 reference standard spot, does not exceed that of the standard solution	TLC, comparison of drug product with 50□g / mL reference standard solution STP# _____	Test completed prior to release of drug product
Residual solvents[4] 1. Acetonitrile 2. Diethyl Ether 3. Ethanol	1. NMT[2] 0.04% (w/v) 2. NMT[2] 0.5% (w/v) 3. NMT[2] 0.5% (w/v)	Gas chromatography, flame ionization detection STP# _____	Test completed prior to release of drug product
2-Chloro-2-deoxy-D-glucose (if it is a possibility in synthesis)	NMT[2] 1.0 mg / *V*[3]	HPLC STP# _____	Validation and on annual batch thereafter
Membrane Filter Integrity	Specify limit for the filter being used	Bubble point measurement STP# _____	Test completed prior to release of drug product
Bacterial endotoxins (LAL)	NMT 175/V USP EU mL of the injection, in which V is the maximum recommended total dose in mL, at the expiration time	STP# _____	State schedule
Sterility testing	Sterile	STP# _____	Test initiated within 24 hours of preparation
Osmolality	Isotonic (specify range)	STP# _____	Validate /

			calculate
Glucose	NMT ___ mg/V^3	No test performed	Calculated based on the amount of mannose triflate used

1. NLT = No Less Than
2. NMT = No More Than
3. *V* = Total volume of the batch of fludeoxyglucose F 18 injection produced
4. Acceptance criteria should assure that the amount of each residual solvent impurity administered to a human subject is within the limits provided in the ICH Guidance on Impurities: residual solvents (Federal Register dated December 24, 1997, Vol. 62, No. 247, Pages 67377 – 67388).

[Note: If a stabilizer is added, test for the assay of stabilizer should be included in the specifications]

9. DESCRIPTION OF ANALYTICAL TEST PROCEDURES

The relevant validated test procedures (STPs) for each test are provided as described below.

Note: Each procedure, at a minimum, should include the following: (1) the analytical supplies and their quality used; (2) all the equipment and the settings used during the performance of the procedure; (3) the preparation of test, standard, and analytical solutions; (4) detailed description of the test procedure; (5) exact calculations performed in quantitative procedures; (6) the recording of the results; and (7) the system suitability test performed (including schedule, the system suitability standards used, and the acceptance criteria to ensure proper performance of the equipment).

Test	STP document #	Attachment	Page number
Appearance			
Radionuclidic identity			
Radiochemical identity and purity			
Radinuclidic purity			
Assay (radioactivity concentration)			
PH			
Test for kryptofix 222			
Test for residual solvents			
2-Chloro-2-Deoxy-D-glucose			
Membrane filter integrity test			
Bacterial endotoxins (LAL)			
Sterility test			

Osmolality			

For chromatographic, spectroscopic (e.g., gamma), and microbiologic procedures, validation data to show suitability of the test procedure for the intended purpose are included in attachment _____, page _____.

10. MICROBIOLOGICAL VALIDATION

This part of the application describes the information you should include in Section 10 (microbiological validation) of your application for PET drug products. At the end of this section, there is a table of contents that you can use to list the information included in your application.

The microbiological validation section of the application should be used to describe the procedures that ensure sterility of injectable PET radiopharmaceuticals. Information common to other sections should be provided directly, and not by reference, to other sections because the microbiological validation attachment is reviewed separately from the chemistry section by microbiology reviewers. The introduction to this section should describe the product's container and closure system (size, shape, and composition), and the time and maximum volume of product solution that may be administered to a patient. Additionally, each of the following issues should be addressed in the microbiology section:

- Manufacturing Site. The manufacturing site (name and complete address) should be identified and accompanied by a description of the manufacturing area. The description should include the presence of environmental controls (e.g., laminar air flow hoods, biosafety cabinets, isolators) that protect product components from microbiological sources of contamination.

- Processing Equipment and Components. The methods for preparing equipment and components should be summarized in the submission. When sterile vials, syringes, transfer sets, and filters are obtained from commercial sources and used in the product's manufacture, a Certificate of Analysis from the suppliers may be substituted where appropriate. Reusable equipment that contacts the PET drug solution during its manufacture should be prepared to eliminate endotoxins and sanitized (or sterilized) to control bioburden. If components are sterilized at the PET facility, their sterilization processes and the components' aseptic assembly should be verified experimentally and summarized in application file. For sterilization done on-site, the performance of a sterilizer should be verified periodically and should be described, including a summary of the method and results from the last study. Drug products for parenteral administration must be sterile. PET solutions are usually filtered and aseptically transferred to a sterile, pyrogen-free container (for example, a multiple dose vial). Certain PET products may not use a vial for the finished dosage form, and these require special consideration. Some PET facilities may use a long fluid line to deliver multiple batches of the product solution to a remote area for further processing. These delivery lines should be described in the application, including their preparation and the validation of the duration of use. When special procedures and components are used, their impact on sterility assurance should be described.

- Facility Environmental Controls. A summary of the manufacturing process should address control systems in the work area used for preparing the finished dosage form. The work area should be clean, and the synthesis unit should be in a location that permits materials to be transferred to the aseptic area without adulteration. It is recommended that batch records indicate that sterile components, materials, and equipment are in protective wrapping or containers when transferred into the aseptic area. Also, it is recommended that final containers, filter assembly, sterile fluid lines, vent filters, and needles are sterile, disposable, and for single use only.

- The Aseptic Area. Many facilities have an aseptic area for the transfer of the sterile solution into a

sterile container for the finished product. As appropriate, the application should include descriptions of the aseptic hood, isolator, or other suitable environmental system area used when preparing the finished product. The air classification in the aseptic environment should be specified using standard nomenclature (e.g., ISO or US Fed. Std 209E). Microbiological testing of the aseptic environment should be done periodically, and the microbiological methods (sampling methods and frequency, culture media, incubation time and temperature) described. These methods may include swabs or contact plates for surfaces, and settle plates or dynamic air samplers. Airborne, non-viable particle counting should be summarized as part of the testing program, although these tests may be done less frequently than microbiological testing.

- Aseptic Technique. The qualification program for aseptic area operators should be summarized in the application. The aseptic techniques used to make a sterile product should be evaluated by process simulation studies. Simulations should be done 3 times to qualify a new operator. Each operator should repeat one simulation annually, or anytime changes occur in the procedures. Microbiological methods, acceptance criteria and results of these simulations (initial studies, or the last annual study) should be provided.

- Filtration Process Qualification. Sterilizing filtration is a critical procedure for removing microorganisms from solutions of injectable PET radiopharmaceuticals. When the filters are made and sterilized by a commercial filter manufacturer, the filtration conditions of pressure and flow rate are generally provided by the filter manufacturer. A certificate from the manufacturer is acceptable, but the filtration conditions such as pressure or volume should be identified in the batch record and not exceeded. Filter integrity tests to demonstrate that the membrane and housing have not lost the ability to retain microorganisms may be done according to the manufacturer's recommended method. An alternative filter integrity test method may be used if it is demonstrated to be acceptable. The batch record should indicate that after filtering the PET radiopharmaceutical, the sterilizing membrane filter is tested for integrity before the product is released. Filter integrity test methods and acceptance criteria should be described in the application.

- Finished Product Microbiological Testing. All products for parenteral administration, including PET radiopharmaceuticals, must be sterile and free of endotoxins (USP <1>, Injections). Sterility and endotoxin tests should be initiated promptly after preparing the product (21 CFR 211.167(a)). Test methods should be described (or provided by a reference) in the application. Details of the methods should include sampling method, sample sizes, microbiological methods, acceptance criteria and actions following a failure. The acceptance limit for endotoxins test results should also include the calculations that relate the patient dose to the endotoxins limit.

You can use the following as a table of contents for the information you include in Section 10 on microbiological validation.

Test or Criterion	Document(s)	Page Number(s)
Product Summary		
Container and Closure System		
Maximum Volume of Patient Dose		
Facility Description		
Sterile Equipment and Components		
Single Use	Certificate of Analysis	
Reusable	Sterilization Validation	
Environmental Controls		
Aseptic Area Environmental Monitoring		
Aseptic Process Simulation Methods and Results		
Sterile Filtration Process		
Microbial Retention Test or Certificate		
Pressure and Flow Rate Limits		
Filter Integrity Test Method		
Post-Use Integrity Test Limits		
Sterility Test Methods, Limits and Controls		
Actions if Test Fails		
Endotoxins Test Methods, Limits and Controls		
Determination of Endotoxins Limit		
Actions if Test Fails		

11.STABILITY AND BATCH DATA

A. EXPIRATION DATING PERIOD

We propose an expiration-dating period of _____ hours from the EOS calibration time when fludeoxyglucose F 18 injection is stored at _____°C +/- ____°C (or controlled room temperature). (Note: Refer to USP for controlled room temperature definition)

B. STABILITY DATA/BATCH DATA

If the submission is an NDA (under section 505 (b)(2) of the act), complete release and stability data on three batches of fludeoxyglucose F 18 injection prepared at the upper range of proposed radioconcentration and stored at _____°C +/- ____°C, are provided in attachment _____, page _____ .

If the submission is an ANDA (under section 505(j) of the act), complete release data on three batches prepared at the upper range of proposed radioconcentration along with the stability data on one of the three batches of fludeoxyglucose F 18 injection prepared at the upper range of proposed radioconcentration and stored at _____°C +/- ____°C, are provided in attachment _____, page _____ .

Additionally for each stability batch,

- The entire batch was stored in the same container/closure as it was produced._____Yes.
- The vial was stored in an inverted position. _____Yes.
- All tests indicated in the specification section were performed at release. _____Yes.
- The appearance, radiochemical purity, radionuclidic purity, and pH (and stabilizer concentration when present) were also evaluated at the end of proposed expiration dating period._____Yes.

[Note: If the application incorporates multiple manufacturing sites, please discuss with the reviewing division in advance of submitting the application concerning the stability and batch data that should be submitted. The phone number for the Division of Medical Imaging and Radiopharmaceutical Drug Products is (301) 827-7510.]

C. POSTAPPROVAL COMMITMENTS

We commit that; annually post-approval a minimum of one batch of fludeoxyglucose F 18 injection will be tested according to the protocol described below. The entire content of the batch vial will be stored inverted at _____ °C for _____ hours (from EOS), and tested according to the specifications and procedures described in this application for finished product testing. The results of such testing will be provided to the FDA in the annual report.

Test	Test performed at Release	Test performed at the end of expiry
Appearance	YES	YES
Radionuclidic identity	YES	NO
Radiochemical identity and purity	YES	YES
Radiochemical impurities	YES	YES
Radionuclidic purity	YES	YES
Assay (radioconcentration)	YES	NO
PH	YES	YES
Test for kryptofix 222 (or other catalyst)	YES	NO
Test for residual solvents	YES	NO