Attachment I

Sample Formats—
Application To Manufacture

Ammonia N 13 Injection
Fludeoxyglucose F 18 Injection (FDG F 18)
and
Sodium Fluoride F 18 Injection

Chemistry, Manufacturing, and Controls Section

These sample applications (chemistry, manufacturing, and controls section) have been prepared by the Office of New Drug Chemistry and the Office of Generic Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration. This document represents the Agency's current thinking on the manufacture of this positron emission tomographic (PET) drug product. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statues, regulations, or both.

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Ammonia N 13 Injection
CMC Sections

Ammonia N 13 Injection

1. DRUG PRODUCT COMPONENTS AND QUANTITATIVE COMPOSITION

Component	Composition/mL	Composition/ batch sub-portion vial
Drug Substance AMMONIA N 13	____ 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)	_____ (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. TARGET MATERIAL (Starting material)

The following target material will be used for the production of ammonia N13:
[Note: If multiple components are used in the target, include the one(s) that undergoes nuclear reaction to produce drug substance.]

1.	Name of the target material	
2.	Name and address of the target material manufacturer	
3.	Tests and acceptance criteria [Tests, procedures and acceptance criteria to control identity, purity, relevant 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 COA 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_____.

B. OTHER INGREDIENTS

The following other ingredients are used in the formulation of finished ammonia N 13 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 _____.]

C. 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 ammonia N 13 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 ____.

[Note: Information concerning additional ingredients is provided in attachment _____, page _____.]

3. REFERENCE STANDARDS

The following reference standards are used in the quality control methods of ammonia N 13 injection:
[Note: 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 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	Ammonium chloride		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 ammonia N 13:
Provide below the name of each component used in the production of ammonia N 13, 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

B. PRODUCTION OF RADIONUCLIDE

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

The following particle accelerator is used for the production of ammonia N 13:

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 (identify for batch or sub-portion, as appropriate)
- 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 Synthesis and Purification Equipment

A description of the synthesis and purification equipment, including a complete schematic flow diagram, is provided in attachment _____, page _____.

The following information should be provided if a commercial unit is used:
Make _____
Model _____

(ii) Description of Synthesis and Purification Operation

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

[Note: Description should also include preparation and manipulation of sub-portions]

(iii) In-Process Controls

The synthesis and purification procedure is controlled by monitoring the in-process parameters described in attachment _____, page_____.

The above controls are monitored and documented in the master production and controls records:
___ Yes.

(iv) Post-Synthesis Procedures

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

6. MANUFACTURE OF DRUG PRODUCT

A. PRODUCTION OPERATION

The synthesized and purified drug substance obtained from the synthesis and purification is collected in the final product vial. The specific procedures used in the formulation and preparation of the finished drug product are provided in attachment _____, page _____.

A copy of the master production and control records, which provide the specific procedures used in the production of and ensure full traceability of all components, materials and equipment used for each batch of ammonia N 13 injection, is provided in attachment _____, page _____.

B. REPROCESSING OF PET DRUG PRODUCT

A manufactured PET drug product batch or lot (or sub-portion thereof) will not be reprocessed.
A manufactured PET drug product batch or lot (or sub-portion thereof) 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 the master production and control records on page _____ (attachment _____). The specifications and acceptance criteria for each lot are provided in attachment _____, page _____.

7. CONTAINER/CLOSURE

C 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.

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

C 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 specification and criteria used for accepting a lot of container/closure is 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 ammonia N 13 injection consists of up to _____ sub-portions, where each sub-portion is produced in one new vial and the entire batch is produced in multiple vials.

To ensure that each batch (i.e., all sub-portions) meets the finished product acceptance criteria; the following vials are tested for the quality control:

9 The first and the last vial (sub-portions) obtained for each batch.
9 The first vial obtained for each batch; we have validated that _____ sub-portions produced in a batch are equivalent. The data to demonstrate equivalency of the above number of sub-portions on three production batches (test sample obtained from beginning, middle and end) are provided in attachment _____, page _____.

B. REGULATORY SPECIFICATIONS, PROCEDURES, AND TESTING SCHEDULES

Each batch of the ammonia N 13 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(s). In the event that a 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# _____	Each sub-portion of a batch is tested
Radionuclidic identity	The measured half-life is between 9.5 – 10.5 minutes.	Measurement of radioactivity for decay of a sample over 10 minute period STP# _____	Quality control sub-portion; testing for first sub-portion completed prior to preparation of clinical sub-portions
Radiochemical identity	The retention time (Rt) of major peak in test solution corresponds (± 5%) with the retention time peak obtained for the reference standard solution.	HPLC STP#_____	Quality control sub-portion; testing for first sub-portion completed prior to preparation of clinical sub-portions
Radionuclidic purity	State limit	Gamma spectroscopy of decayed sample STP# _____	State periodic schedule
Radiochemical purity	NLT[1] 95.0 % ammonia N 13	HPLC STP#_____	Quality control sub-portion; testing for first sub-portion for first sub-portion completed prior to preparation of clinical sub-portions
Assay (radioactivity concentration)	____mCi to ____ mCi / mL @ EOS for each sub-portion (vial)	USP STP# _____	Each sub-portion
Specific activity	NLT[1] 10 Ci / mmol	HPLC STP# _____	State schedule
PH	4.5 – 7.5 (USP)	pH paper with pH reference standards STP# _____	Quality control sub-portion or each sub-portion (depending of production method); testing for first sub-portion completed prior to

			release
Membrane filter integrity	Specify limit for the filter being used.	Bubble point measurement STP# _____	State schedule for each sub-portion.
Bacterial endotoxin (LAL)	NMT[2] 175/V USP EU mL of the injection, in which V is the maximum recommended total dose in mL, at the expiration time	STP# _____	Quality control sub-portion; testing for first sub-portion completed prior to release
Sterility Testing	Sterile	STP# _____	Quality control sub-portion; test initiated within 24 hours of preparation.
Osmolality	Isotonic (specify range)	STP# _____	Validate / calculate
Chemical purity (provide tests for appropriate chemical impurities based on the specific method of preparation)	State limits for each	State method and provide STP# STP# _____	Quality control sub-portion; testing for first sub-portion completed prior to preparation of clinical sub-portions

1. NLT = No Less Than
2. NMT = No More Than

9. DESCRIPTION OF ANALYTICAL TEST PROCEDURES

The 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 performance schedule, 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)			
Specific activity			
PH			
Radiochemical impurities			
Specific activity			
Membrane filter integrity test			
Bacterial endotoxin (LAL)			
Sterility test			
Osmolality			
Chemical purity [identify specific test(s)]			

For chromatographic, radionuclidic purity, and microbial procedures, validation data to show the 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 _____ minutes/hours from the EOS calibration time when ammonia N 13 injection is stored at _____^{o}C +/-____^{o}C.
[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 ammonia N 13 injection, prepared at the upper range of proposed radioactivity concentration and stored at _____^{o}C +/- ____^{o}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 radioactivity concentration along with the stability data on one of the three batches of Ammonia N 13 injection, prepared at the upper range of proposed radioactivity concentration and stored at _____^{o}C +/- ____^{o}C, are provided in attachment _____, page _____ .

Additionally for each stability batch,

- The 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 Product is (301) 827-7510.]

C. POSTAPPROVAL COMMITMENTS

We commit that; annually post-approval a minimum of one batch of ammonia N 13 injection will be tested according to the protocol described below. The entire content of the batch vial will be stored inverted at _____ ^{o}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
Radionuclidic purity	YES	YES
Assay (radioactivity concentration)	YES	NO
pH	YES	YES
Specific activity	YES	YES
Radiochemical	YES	NO

impurities		
Chemical purity	YES	NO
Membrane filter integrity test	YES	NO
Bacterial endotoxin (LAL)	YES	NO
Sterility test	YES	NO
Osmolality	YES	NO

Additionally, we commit that any batch or sub-portion thereof of ammonia N 13 injection that fails to meet the acceptance criteria will not be released or, if already distributed, will be withdrawn from the market.

We also commit that FDA will be notified of any changes to the approved application, beyond the variations already provided for in the application and that any such change will be implemented according to the requirements under section 506A of the Food and Drug Modernization Act and/or 21CFR 314.70 and 21 CFR 314.71 (for NDA) or under 21CFR 314.97 (for ANDA), as applicable.

12. VIAL AND OUTER PACKAGING LABELS

Draft copies of proposed vial and outer packaging labels are provided in attachment _____, page _____.

13. ENVIRONMENTAL ASSESSMENT

In accordance with 21 CFR 25.31(b), the (insert name of sponsor) claims a categorical exclusion from the environmental assessment requirements of 21 CFR 25.20 for approval of ammonia N 13 Injection on the basis that the estimated concentration of ammonia N 13 at the point of entry into the aquatic environment will be below 1 part per billion. Additionally, to (name of sponsor)'s knowledge no extraordinary circumstances exist.

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: _____^{o}C to _____^{o}C for _____minutes.

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

  The reaction vessel is heated between _____^{o}C to _____^{o}C for _____minutes.

- Temperature and duration of the hydrolysis reaction.
  The reaction vessel is heated between _____^{o}C to _____^{o}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 _____^{o}C +/- ____^{o}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 _____^{o}C +/- ____^{o}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 _____^{o}C +/- ____^{o}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 _____ ^{o}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

2-Chloro-2-deoxy-D-glucose	YES	NO
Membrane filter integrity test	YES	NO
Bacterial endotoxins (LAL)	YES	NO
Sterility test	YES	NO
Osmolality	YES	NO

(Note: Include stabilizer at both time intervals, if present)

Additionally, we commit that any batch of fludeoxyglucose F 18 injection that fails to meet the acceptance criteria will not be released or, if already distributed, will be withdrawn from the market.

We also commit that FDA will be notified of any changes to the approved application, beyond the variations already provided for in the application, and that any such change will be implemented according to the requirements under section 506A of the Food and Drug Modernization Act and/or 21CFR 314.70 and 21 CFR 314.71 (for NDA) or under 21CFR 314.97 (for ANDA), as applicable.

12. VIAL AND OUTER PACKAGING LABELS

Draft copies of proposed vial and outer packaging labels are provided in attachment _____, page _____.

13. ENVIRONMENTAL ASSESSMENT

In accordance with 21 CFR 25.31(b), the (insert name of sponsor) claims a categorical exclusion from the environmental assessment requirements of 21 CFR 25.20 for approval of fludeoxyglucose F 18 injection on the basis that the estimated concentration of 2-deoxy-2[^{18}F]fluoro-D-glucose at the point of entry into the aquatic environment will be below 1 part per billion. Additionally, to (name of the sponsor)'s knowledge no extraordinary circumstances exist.

Sodium Fluoride F 18 Injection
CMC Sections

Sodium Fluoride F 18 Injection

1. DRUG PRODUCT COMPONENTS AND QUANTITATIVE COMPOSITION

Component	Composition/mL	Composition/batch
Drug Substance Sodium Fluoride F 18	____ 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)	_____ (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. TARGET MATERIAL (Starting material)

We will produce the fluoride F 18 drug substance 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 production

1.	Name of the target material	[^{18}O] Water
2.	Name and address of the target material manufacturer	
3.	Tests and acceptance criteria [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 COA 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 should be provided in attachment _____, page _____.

(ii) **DRUG SUBSTANCE:** We will obtain drug substance from other sources, for the production sodium fluoride F 18 injection: _____Yes _____No.

If yes, for each source, the following information is provided in a Type-II Drug Master File (DMF). The sponsor should refer to the "Guideline for Drug Master Files" for the administrative information that should be included in the DMF.

- Name and composition of the fluoride F 18.
- Name and address of the manufacturer.
- Details of the method of manufacture including the controls for the components and raw materials.
- Tests, acceptance criteria, testing procedures, and procedures used to accept and release each lot of fluoride F 18 solution for the production of sodium fluoride F 18 Injection.
- Information on the container/closure in which the fluoride F18 drug substance is supplied, and the copy of the label affixed to it.
- Representative certificates of analysis (that would be sent to the purchaser with each lot) on three representative lots of Fluoride F 18 solution received by sponsor and used in the production of sodium fluoride F 18 Injection.
- Claim for categorical exclusion from the environmental assessment requirements.

The data and information are provided in DMF # _____. A letter of authorization from the drug substance DMF holder, authorizing FDA to refer to the DMF in connection with our application, is provided in attachment _____, page _____.

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

If yes, for each additional supplier, the above information is provided in attachment _____, page _____.

B. OTHER INGREDIENTS

The following other ingredient(s) are used in the formulation of finished sodium fluoride 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 _____.

C. REAGENTS, SOLVENTS, GASES, PURIFICATION COLUMNS, AND OTHER AUXILIARY MATERIALS:

Provide following information for each reagent, solvent, gas, purification columns, and other auxiliary materials, which are used in the production of sodium fluoride 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 ____.

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 sodium fluoride F18 injection:

[Note: 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 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	Sodium Fluoride		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

NOTE: If fluoride F 18 is obtained from external sources, the drug substance manufacturing information (item 5) should be provided in the drug master file referenced in 2.A (ii) above.

A. BATCH FORMULA The following components and their quantities are used in the production of each batch of fluoride F 18:

Provide below the name of each component used in the production of fluoride F 18, 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

B. PRODUCTION OF RADIONUCLIDE

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

The following particle accelerator is used for the production of fluoride F 18

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 Synthesis and Purification Equipment

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

(ii) Description of Synthesis and Purification Operation

A step-wise description of the synthesis and purification procedure is provided in attachment _____, page _____.

(iii) In-Process Controls

The synthesis and purification procedure is controlled by monitoring the in-process parameters described in attachment _____, page___.

All stated 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 specific procedures used in the formulation and preparation of the 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 sodium fluoride 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 each lot 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 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 sodium fluoride 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, descriptions of the amount of volume that is withdrawn from the finished drug product container and how it is distributed among individual tests are provided in attachment _____, page _____.

(ii) If each batch is produced in multiple vials, a description of sampling techniques that ensure 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 sodium fluoride 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 a sample in a dose calibrator over 10 minute period STP# _____	Test completed prior to release of drug product
Radiochemical identity	The Rt of drug product test solution corresponds (+/- 10%) to the Rt of sodium fluoride reference standard	Chromatography (e.g., HPLC) STP#_____	Test completed prior to release of drug product
Radionuclidic purity	State limit (refer to USP)	Gamma spectroscopy of decayed sample STP# _____	State schedule
Radiochemical purity	NLT[1] 95% fluoride F 18	Chromatography (e.g., HPLC) STP#_____	Test completed prior to release of drug product
Assay (Radioactivity concentration)	____mCi to ____ mCi / mL @ EOS (This should be same as stated strength of drug product)	See USP STP# _____	Test completed prior to release of drug product
Specific activity	No carrier added	None, prepared by no carrier method of synthesis	No testing performed
PH	6.0 – 8.0	pH paper with pH reference standards STP# _____	Test completed prior to release of drug product
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
			Test initiated

Sterility testing	Sterile	STP# _____	within 24 hours of preparation
Osmolality	Isotonic (specify range)	STP# _____	Validate / Calculate

1. NLT = No Less Than

[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 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			
Membrane filter integrity test			
Bacterial endotoxins (LAL)			
Sterility test			
Osmolality			

For chromatographic, spectroscopic (e.g., gamma), and microbiologic procedures, appropriate validation data to show the 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 sodium fluoride F 18 injection is stored at _____^{o}C +/- ____^{o}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 sodium fluoride F 18 injection prepared at the upper range of proposed radioconcentration and stored at _____^{o}C +/- ____^{o}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 sodium fluoride F 18 injection prepared at the upper range of proposed radioconcentration and stored at _____^{o}C +/- ____^{o}C, are provided in attachment _____, page _____ .

Additionally for each batch,

- The 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 sodium fluoride F 18 will be tested according to the protocol described below. The entire content of the batch vial will be stored

inverted at _____ ^{o}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
Radionuclidic purity	YES	YES
Assay (Radioactivity concentration)	YES	NO
PH	YES	YES
Membrane filter integrity test	YES	NO
Bacterial endotoxins (LAL)	YES	NO
Sterility test	YES	NO
Osmolality	YES	NO

(Note: Include stabilizer at both time intervals, if present.)

Additionally, we commit that any batch od sodium fluoride F 18 injection that fails to meet the acceptance criteria will not be released or if already distributed will be recalled from the market.

We also commit that FDA will be notified of any changes to the approved application, beyond the variations already provided for in the application, and that any such change will be implemented according to the requirements under section 506A of the Food and Drug Modernization Act and / or 21CFR 314.70 and 21 CFR 314.71 (for NDA) or under 21CFR 314.97 (for ANDA), as applicable.

12. VIAL AND OUTER PACKAGING LABELS

Draft copies of proposed vial and outer packaging labels are provided in attachment _____, page _____.

13. ENVIRONMENTAL ASSESSMENT

In accordance with 21 CFR 25.31(b), the (insert name of sponsor) claims a categorical exclusion from the environmental assessment requirements of 21 CFR 25.20 for approval of sodium fluoride F 18 injection on the basis that the estimated concentration of sodium fluoride F18 at the point of entry into the aquatic environment will be below 1 part per billion. Additionally, to (name of sponsor)'s knowledge no extraordinary circumstances exist.