Attachment I

Sample Formats—

Chemistry, Manufacturing, and Controls (CMC) Section

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

Date: August 2011

These sample formats for the chemistry, manufacturing, and controls section have been prepared by the PET Steering Committee in the Center for Drug Evaluation and Research at the Food and Drug Administration. This document represents the Agency's current thinking on the production of these positron emission tomography (PET) drug products. 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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INSTRUCTIONS

1. At a number of places, the sample format contains text that provides guidance to assist you in the preparation of the CMC section of your NDA or ANDA. Such text is in "*italics*", and may be omitted in the submitted NDA or ANDA.

2. Where necessary, the CMC section may be expanded or contracted to include additional or less information, respectively.

Ammonia N 13 Injection
CMC Sections

Ammonia N 13 Injection

1. DRUG PRODUCT COMPONENTS AND QUANTITATIVE COMPOSITION

Component	Composition/mL	Composition/ sub-batch vial
Drug Substance Ammonia N 13	____ to ____ mCi @ EOS[1] (____ to ____ MBq @EOS)	____ to ____ mCi @ EOS[1] (____ to ____ MBq @EOS)
Inactive 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 inactive ingredients used in drug product. Examples of inactive ingredients include diluents, buffers, stabilizers, and preservatives.*

2. CONTROLS FOR COMPONENTS AND OTHER 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.	Specifications *[Specifications to control identity, purity, relevant quality should be proposed]*	TEST ACCEPTANCE CRITERION TEST PROCEDURE Attachment _____, page _____.
4.	Identity test performed to release each lot for production use	TEST PROCEDURE ACCEPTANCE CRITERION _____ _____ _____ The procedure is provided in attachment _____, page_____.
	Certificate of analysis (COA)	Copy of representative COA is provided in attachment

5.		_____, page_____.
6.	Is the target material recycled?	_____ Yes _____ No. If yes, its reprocessing procedures are described in attachment _____, page_____. Data to support that the reprocessed material conforms to the acceptance criteria for the target material are provided in attachment _____, page____.

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. INACTIVE INGREDIENTS

The following inactive ingredients are used in the ammonia N 13 injection drug product:

Name	Function of the inactive ingredient	Name and address of the manufacturer	Specifications, representative COA and acceptance procedures for each lot are included
			Attachment _____, page ____.
			Attachment _____, page ____.

[Note: COA need not be provided if the inactive ingredient used is a marketed finished drug product.]

Additional inactive ingredients (if any) are listed and the information is 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 procedures for each lot are included
1			Attachment _____, page ____.
2			Attachment _____, page ____.

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

[Note: The above table can be extended, if needed, to include additional raw materials, and information provided in an attachment]

3. REFERENCE STANDARDS

The following reference standards are used in the quality control test 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 procedures for each lot are included
1	Ammonium chloride		Attachment _____, page____

4 PRODUCTION AND TESTING FACILITIES

Name of PET drug production facility: _____
Address: _____
_____
_____
Name of contact person: _____
Phone number of contact person: _____

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

5. PRODUCTION OF DRUG SUBSTANCE

A. BATCH FORMULA

The following components and quantities are used in the production of each batch of ammonia N 13

drug substance:
[Provide the name of each component (include all reactants, solutions, solvents, and reagents used in the chemical synthesis and purification operation) 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]

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, if any, is provided in attachment _____, page _____.

(ii) Operating Parameters

- During irradiation a beam current of _____μA ± ____μA 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 body is _____ μl or ml.
- The target body used in production operation is composed of _____.
- The target windows used in target body 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-batches]

(iii) In-Process Controls

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

[Note: We recommend that the applicant have adequate process controls to ensure continued quality of the product. The specified process controls should be monitored and documented in the master production and control records]

(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. PRODUCTION OF DRUG PRODUCT

A. PRODUCTION OPERATION

The drug substance obtained following the synthesis and purification procedures 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 / accountability of all components, materials and equipment used and the operators for each batch of ammonia N 13 injection, is provided in attachment _____, page _____.

B. REPROCESSING OF PET DRUG PRODUCT

Check below as appropriate and provide the indicated information.

□ A PET drug product batch or lot (or sub-batch thereof) will not be reprocessed.
□ A PET drug product batch or lot (or sub-batch thereof) may be reprocessed under the specific conditions (circumstances) 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 finished drug product vial and the method of labeling are described in the master production and control records on page _____ (attachment _____).

The specifications for the packaging components and acceptance procedures 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 a commercial supplier: _____Yes _____ No.

- If no, 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 procedures used for accepting a lot of 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 this NDA/ANDA, 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-batches, where each sub-batch is produced in one new vial and the entire batch is produced in multiple vials.

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

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

B. REGULATORY SPECIFICATIONS

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 described in the SOPs submitted as part of this NDA / ANDA:

[Note: The following tests are related to a commonly used production method. In the event that a production method does not use a component listed below or uses an alternate method or produces additional impurities, appropriate tests, acceptance criteria, procedures, and testing

schedules that are more appropriate for such production method should be proposed.]

TEST	ACCEPTANCE CRITERIA	TEST PROCEDURE & SOP NUMBER	TESTING SCHEDULE
Appearance	Colorless and free from particulate matter	Visual observation under lighted conditions SOP# _____	Each sub-batch 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 a 10 minute period SOP# _____	Quality control sub-batch; testing for first sub-batch is completed prior to preparation of clinical sub-batches
Radiochemical identity	The retention time (Rt) of major peak in test solution corresponds (e.g., ± 5%) with the retention time peak obtained for the reference standard solution.	HPLC SOP#_____	Quality control sub-batch; testing for first sub-batch is completed prior to preparation of clinical sub-batches
Radionuclidic purity	State limit and provide justification in an attachment. Attachment_____ Page_____	Gamma spectroscopy of decayed sample SOP# _____	State schedule and provide justification Attachment_____ Page_____
Radiochemical purity	NLT[1] 95.0 % Ammonia N 13	HPLC SOP#_____	Quality control sub-batches; testing for first sub-batch for first sub-portion completed prior to preparation of clinical sub-batches
Assay (radioactivity concentration)	____mCi to ____ mCi / mL @ EOS for each sub-batch (vial)	Refer to USP SOP# _____	Each sub-batch
Specific activity	NLT[1] 10 Ci / mmol	HPLC SOP# _____	State schedule / provide justification
PH	4.5 – 7.5 (USP)	pH paper with pH reference standards SOP# _____	Quality control sub-batch or each sub-batch (depending of production

			method); testing for sub-batch is completed prior to final release
Membrane filter integrity	Specify limit for the filter being used.	Bubble point measurement SOP# _____	State schedule for each sub-batch.
Bacterial endotoxin (LAL)	NMT[2] 175 EU/V, in which V is the maximum recommended total dose in mL, at the expiration time. For intrathecal administration, please contact the review division.	Refer to USP SOP# _____	Quality control sub-batch; testing for first sub-batch completed prior to release
Sterility Testing	Sterile	Refer to USP SOP# _____	Quality control sub-batch; test initiated within 24 hours of preparation.
Osmolality	Isotonic (specify range)	SOP# _____	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 SOP. SOP# _____	Quality control sub-batch; testing for first sub-batch is completed prior to preparation of clinical sub-batch

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

9. DESCRIPTION OF ANALYTICAL TEST PROCEDURES

Each standard test procedure should be included and its location in the NDA/ANDA identified below:

[Note: Each procedure 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(s) performed (including performance schedule, system suitability standards used, and the acceptance criteria that ensure proper performance of the equipment). Each procedure should be reliable and capable of providing valid data. Where applicable, the procedure should be specific and stability indicating. For chromatographic, spectroscopic (e.g., gamma) and microbiologic procedures, validation data that show suitability of the test procedure for the intended purpose should be included in the attachment where the test procedure is included.]

Test	Test Procedure Number	Attachment	Page Number
Appearance			
Radionuclidic identity			
Radiochemical identity and purity			
Radinuclidic purity			
Assay (radioactivity concentration)			
Specific activity			
pH			
Membrane filter integrity			
Bacterial endotoxin (LAL)			
Sterility			
Osmolality			
Chemical purity [identify specific test(s)]			

[Note: Above list of test procedures should correspond to the tests proposed as part of the specifications, and the list may be amended as necessary.]

10. MICROBIOLOGICAL VALIDATION

This part describes the information you should submit in Section 10 (microbiological validation) of your NDA/ANDA for PET drug product. At the end of this section, there is a table of contents that you can use to list the information submitted in your NDA/ANDA. The indicated information should be submitted in this part of the CMC section of your NDA/ANDA and the descriptive guidance provided to assist you in this section need not be included.

The microbiological validation section of the CMC section of your NDA/ANDA 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:

- Production Site. *The production site (name and complete address) should be identified and accompanied by a description of the production 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 production, 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 this section. 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 CMC section of your NDA/ANDA, 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 production 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, you should include provide 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 your NDA/ANDA. 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. PET products for parenteral administration must meet their established criteria for sterility and for pyrogens (USP <1>, Injections). Tests (e.g., sterility and endotoxins) should be initiated promptly after preparing the product according to methods described

(or provided by a reference) in your NDA/ANDA. Details of the methods should include sampling method, sample sizes, microbiological methods, acceptance criteria and actions following a failure. An endotoxins assay is an acceptable demonstration of pyrogenic potential. An acceptance criterion for the endotoxins test should be established and documented in the application using the calculations that relate the drug dose to the patient's exposure limit for endotoxins, usually NMT 175 EU/V, where V is the maximum recommended dose in mL (see USP <85>, Bacterial Endotoxins Test). For intrathecal administration, please contact the review division for limits.

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 _____°C +/-____°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 _____ .

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 your NDA/ANDA incorporates multiple production sites, please discuss with the reviewing division in advance of submitting your NDA/ANDA concerning the stability and batch data that should be submitted. The phone number for the Division of Medical Imaging Products is (301) 796-2050]

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 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 proposed 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 impurities	YES	NO
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-batch 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 NDA/ANDA, beyond the variations already provided for in the NDA/ANDA 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)
Inactive 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 inactive ingredients used in drug product. Examples of inactive ingredients include diluents, buffers, stabilizers, and preservatives.*

2. CONTROLS FOR COMPONENTS AND OTHER RAW MATERIALS

A. PRECURSOR [e.g., 1,3,4,6-Tetra-O-acetyl-2-O-trifluoromethanesulfonyl-β-D-mannopyranose (mannose triflate)] – *Considered an intermediate and information concerning its manufacture and controls, under cGMP, should be included either in the application or may be referenced to a Drug Master File (DMF) from your supplier, filed with FDA.*

State the name [e.g., 1,3,4,6-Tetra-O-acetyl-2-O-trifluoromethanesulfonyl-β-D-mannopyranose (mannose triflate)] and provide following information for the precursor used for radiochemical synthesis:

1.	Name of the component	
2.	Name and address of supplier	
3.	Is this raw material further purified on site?	_____ Yes _____ No. If yes, method of purification is provided in attachment _____, page_____.
4.	Specifications *(Specifications that control the identity, purity and quality of each lot should be included)*	TEST / ACCEPTANCE CRITERION / TEST PROCEDURE 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 each lot for production	TEST PROCEDURE ACCEPTANCE CRITERION _____ _____ _____ Detailed test procedure is included in attachment _____, page_____.
7.	Storage conditions	1. Container/closure _____ 2. Stored at _____ 3. This 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 only produce radioactive fluoride reagent on site at the PET drug production facility? _____Yes ____No.

Provide, as appropriate, details in section (i) and / or section (ii) below:

(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 *[Specifications that control identity, purity, and quality of each lot should be included]*	TEST ACCEPTANCE CRITERION TEST PROCEDURE Identity _____ Enrichment Provide justified minimum limit Conductivity Provide justified maximum limit Fluoride Content Provide justified maximum limit Other Attributes that control purity should be included Attachment _____, Page _____. *(Justifications should be included in the attachment)*
4.	Identity test performed to release each lot for production	TEST PROCEDURE ACCEPTANCE CRITERION _____ _____ _____ Detailed test procedure is included in attachment

		_____, page_____.
5.	Certificate of analysis (COA)	Copy of representative certificate of analysis is provided in attachment _____, page_____.
6.	Is the target material recycled?	_____ Yes _____ No. If yes, the reprocessing procedures are described in attachment _____, page_____. Data to support that the reprocessed material conforms to the acceptance criteria for the target material are provided in attachment _____, page _____.

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

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

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

If yes, provide the [^{18}O] Water information as described in (i) above (may be provided in a DMF from the supplier or in your NDA/ANDA), and the following information:

1.	Name and composition of the fluoride reagent solution	
2.	Name and address of qualified supplier	
3.	Method of preparation *(Check the box that applies to your situation)*	1. The fluoride reagent is prepared using a ____MeV particle accelerator utilizing $^{18}O(p, n)^{18}F$ reaction on $H_2{}^{18}O$. 2. The fluoride reagent is reactor produced. If fluoride is produced by methods described in 2, or any other method provide description of the method of preparation, purification, specifications and acceptance procedures that are appropriate for such production method. Information is provided in attachment _____, page_____.
4.	Specifications *(Provide appropriate specifications that control the quality of each lot this material)*	TEST ACCEPTANCE CRITERION TEST PROCEDURE _____ _____ _____ _____ _____ _____ Attachment _____, page _____.

5.	Provide acceptance 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 the fluoride reagent: _____Yes _____No.

If yes, for each additional supplier, the fluoride reagent identified in 1,2,3, and 6 above is provided in attachment _____, page_____. [Note: Fluoride F18 from different sources must meet the sponsor's proposed specifications.]

C. INACTIVE INGREDIENTS

The following inactive ingredient(s) are used in the fludeoxyglucose F 18 injection.

Name	Function of the inactive ingredient	Name and address of the manufacturer	Specifications, representative COA and acceptance procedures for each lot are included
			Attachment ___, page ____.
			Attachment ___, page ____.

[Note: COA need not be provided if the inactive ingredient used is a marketed finished drug product.]

Additional inactive ingredients (if any) are 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 procedures for each lot are included
1			Attachment _____, page ____.

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

[Note: The above table may be extended, if needed, to include additional raw materials, and information provided in an attachment.]

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. 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 should 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 procedures for each lot are included
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. PRODUCTION AND TESTING FACILITIES

Name of PET drug production facility: _____
Address: _____
_____
_____
Name of contact person: _____
Phone number of contact person: _____

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

5. PRODUCTION 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 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-β-D-mannopyranose]		_____ mg ± __mg
[^{18}F]Fluoride	Reagent	_____mCi to _____mCi

B. PRODUCTION OF RADIONUCLIDE

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

If the radioactive fluoride reagent is obtained from outside suppliers, the following information (i, ii, & iii), may be included in supplier's DMF or provided in your NDA/ANDA:

(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 _____μA ± ____μA 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 body is_____ μl or ml.
- The target body used in production operation is composed of _____.
- The target windows used in target body 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

We recommend that the applicant have adequate process controls to ensure continued quality of the product. All controls that are necessary to assure reproducible quality of the drug should be described. The following are examples of the 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 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. PRODUCTION 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 finished drug product are provided in attachment _____, page _____.

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

B. REPROCESSING OF PET DRUG PRODUCT

Check below as appropriate and provide the indicated information.

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

□ A PET drug product batch or lot may be reprocessed under the specific conditions (circumstances) 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 for the packaging component(s) and the acceptance procedures 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 a commercial supplier._____Yes _____ No.

- If no, 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 procedures used for accepting a 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 NDA/ANDA, 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 *(check, as appropriate)*:

- 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 how the representative sample is obtained (e.g., 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

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 submitted 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 or produces additional impurities, appropriate tests, acceptance criteria, procedures, and testing schedules that are more appropriate for such production method should be proposed.]

TEST	ACCEPTANCE CRITERIA	PROCEDURES	TESTING SCHEDULE
Appearance	Colorless and free from particulate matter	Visual observation under lighted conditions SOP# _____	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 minute period SOP# _____	Test completed prior to release of drug product
Radiochemical identity	The Rf of 2-deoxy-2[^{18}F]fluoro-D-glucose corresponds (e.g., < $\pm$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 and by treatment with appropriate reagent) SOP#_____	Test completed prior to release of drug product
Radionuclidic purity	State limit and provide justification in an attachment. Attachment_____ Page_____	State suitable method of analysis of decayed sample SOP#_____	State schedule and provide justification Attachment____ Page_____
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 (TLC scanned in a radio-chromatographic scanner) SOP#_____	Test completed prior to release of drug product
Radiochemical impurities	State the maximum limit for fluoride F 18 (free) and provide justification. Attachment_____ Page_____	Provide test procedure SOP# _____	Test completed prior to release of drug product

Assay (radioactivity concentration)	____mCi to ____ mCi / mL @ EOS (This should be same as the stated strength of drug product)	Refer to USP SOP#_____	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 added method of synthesis	No testing performed
pH	Specify justified limits Attachment_____ Page_____	pH paper with pH reference standards SOP# _____	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 50μg/ml kryptofix 222 reference standard spot, does not exceed that of the standard solution	TLC, comparison of drug product with 50 μg / mL reference standard solution SOP# _____	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 SOP# _____	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 SOP# _____	Validation and on annual batch thereafter
Membrane Filter Integrity	Specify limit for the filter being used	Bubble point measurement SOP# _____	Test completed prior to release of drug product
Bacterial endotoxins (LAL)	NMT[2] 175 EU/V, in which V is the maximum recommended total dose in mL, at the expiration time. For intrathecal administration, please contact the review division.	State test procedure SOP# _____	Test completed prior to final release of drug product
Sterility testing	Sterile	State test procedure SOP# _____	Test initiated within 24 hours of preparation
Osmolality	Isotonic (specify range)	SOP# _____	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

Each standard test procedure and its location in the NDA / ANDA are identified below:

[Note: Each procedure 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(s) performed (including performance schedule, system suitability standards used, and the acceptance criteria that ensure proper performance of the equipment). Each procedure should be reliable and capable of providing valid data. Where applicable, the procedure should be specific and stability indicating. For chromatographic, spectroscopic (e.g., gamma) and microbiologic procedures, validation data that show suitability of the test procedure for the intended purpose should be included in the attachment where the test procedure is included.]

Test	Test Procedure Number	Attachment	Page Number
Appearance			
Radionuclidic identity			
Radiochemical identity and purity			
Radinuclidic purity			
Assay (radioactivity concentration)			
pH			
Test for kryptofix 222 (if used in synthesis)			
Residual solvents			
2-Chloro-2-Deoxy-D-glucose			
Membrane filter integrity test			
Bacterial endotoxins (LAL)			
Sterility test			

Osmolality			

[Note: Above list of test procedures should correspond to the tests proposed as part of the specifications, and the list may be amended as necessary]

10. MICROBIOLOGICAL VALIDATION

This part describes the information you should submit in Section 10 (microbiological validation) of your NDA/ANDA for the PET drug product. At the end of this section, there is a table of contents that you can use to list the information submitted in your NDA/ANDA. Only the indicated information should be submitted in this section and the descriptive guidance provided to assist you need not be included.

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:

- Production Site. *The production site (name and complete address) should be identified and accompanied by a description of the production area. The description should include the presence of environmental controls (e.g., laminar airflow 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 production, 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 CMC section of your NDA/ANDA, 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 production 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, you should provide 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 your NDA/ANDA. 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. Integrity testing by the drug manufacturer is not intended to confirm the filter porosity rating, as is the filter manufacturer's testing. However, in-process 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 or by an alternative filter integrity test method that demonstrates the filter membrane is not torn or detached from the housing. 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. Test methods should be described (or provided by a reference) in your NDA/ANDA. 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 production 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 Products is (301) 796-2050.]

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 proposed expiry
Appearance	YES	YES
Radionuclidic identity	YES	NO
Radiochemical identity and purity	YES	YES
Radiochemical impurities (free ^{18}F fluoride)	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 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)
Inactive 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 inactive ingredients used in drug product. Examples of inactive ingredients include diluents, buffers, stabilizers, and preservatives.*

2. CONTROLS FOR COMPONENTS AND OTHER 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.	Specifications *[Specifications that control identity, purity, and quality of each lot should be included]*	TEST — ACCEPTANCE CRITERION — TEST PROCEDURE Identity _____ _____ Enrichment Provide justified minimum limit Conductivity Provide justified maximum limit Fluoride Content Provide justified maximum limit Other Attributes that control purity should be included Attachment _____, Page _____. (Justifications should be included in the attachment)
4.	Identity test performed to release each lot for production	TEST PROCEDURE ACCEPTANCE CRITERION

		_____ _____ _____ The test procedure is included in attachment _____, page _____.
5.	Certificate of analysis (COA)	Copy of representative COA is provided in attachment _____, page_____.
6.	Is the target material recycled?	_____ Yes _____ No. If yes, its reprocessing procedures are described in attachment _____, page_____. Data to support that the reprocessed material conforms to the acceptance criteria for the target material are provided in attachment _____, page_____.

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

If yes, for each additional supplier, the target material information identified in items 1, 2, and 5 above should be provided in attachment _____, page _____.

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

If yes, for each source, the following information should 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 used in its manufacture.*
- *Specifications for the release of fluoride F 18 drug substance.*
- *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 drug substance 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 _____.

When fluoride f 18 drug substance is obtained from other (e.g., outside) suppliers, the drug application should contain the acceptance procedures used by the PET drug product producer to accept and release each lot for PET drug product production. Accordingly, following information should be supplied in the application:

1.	Name and composition of the fluoride reagent solution	

2.	Name and address of qualified supplier	
3.	Method of preparation	1. The fluoride F 18 is prepared using a ____MeV particle accelerator utilizing $^{18}O(p, n)^{18}F$ reaction on $H_2{}^{18}O$:_____Yes *If fluoride reagent is produced by other methods (e.g., reactor produced), additional information appropriate to such method of production may be necessary. This should be discussed in advance with the reviewing division.*
4.	Specifications *(Provide specifications that control the quality of each lot this material)*	TEST ACCEPTANCE CRITERION TEST PROCEDURE _____ _____ _____ _____ _____ _____ Attachment _____, page _____.
5.	*Provide* acceptance 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 the fluoride F18: _____Yes _____No.

If yes, for each additional supplier, the fluoride F 18 information identified in 1, 2, 3, and 6 above is provided in attachment _____, page_____. *[Note: Fluoride F18 from different sources must meet the sponsor's proposed specifications]*

B. INACTIVE INGREDIENTS

The following inactive ingredient(s) are used in sodium fluoride F 18 injection.

Name	Function of the inactive ingredient	Name and address of the manufacturer	Specifications, representative COA and acceptance procedures for each lot are included
			Attachment _____, page ____.
			Attachment _____, page ____.

Note: COA need not be provided if the inactive ingredient used is a marketed finished drug product.

Additional inactive ingredients*, if any,* are 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 procedures for each lot are included
1			Attachment _____, page ____.
2			Attachment _____, page ____.
3			Attachment _____, page ____.
4			Attachment _____, page ____.
5			Attachment _____, page ____.

[Note: The above table may be extended, if needed, to include additional raw materials, and information provided in an attachment]

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 should 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 procedures for each lot are included
1	Sodium Fluoride		Attachment _____, page ____.

4. PRODUCTION 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. PRODUCTION 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 _____μA ± ____μA 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 body is _____ μl or ml.
- The target body used in production operation is composed of _____.
- The target windows used in target body 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

We recommend that the applicant have adequate process controls to ensure continued quality of the product. The production procedure is controlled by monitoring the process controls and parameters described in attachment _____, page___.

All stated 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 specific procedures used in the production of and ensure full traceability / accountability of all components, materials and equipment used, and the operators for each batch of sodium fluoride F 18 injection are provided in attachment _____, page _____.

B. REPROCESSING OF PET DRUG PRODUCT

Check below as appropriate and provide the indicated information:

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

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

The validated procedures 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 for the packaging components and the acceptance procedures 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 a 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 the procedures used for accepting a 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 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,* a description of how the representative sample is obtained (e.g., 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 ensure that

the test sample is representative of the entire batch is provided in attachment _____, page _____.

B. REGULATORY SPECIFICATIONS

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 described in the SOPs submitted 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 method should be proposed.]

TEST	ACCEPTANCE CRITERIA	PROCEDURES	TESTING SCHEDULE
Appearance	Colorless and free from particulate matter	Visual observation under lighted conditions SOP# _____	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 a10 minute period SOP# _____	Test completed prior to release of drug product
Radiochemical identity	The retention time (R_t) of drug product test solution corresponds (e.g., < $\pm$10%) to the R_t of sodium fluoride reference standard	State specific chromatography procedure SOP#_____	Test completed prior to release of drug product
Radionuclidic purity	State limit and provide justification in an attachment Attachment_____ Page_____	State suitable method of analysis of decayed sample SOP# _____	State schedule and provide justification Attachment____ Page_____
Radiochemical purity	NLT[1] 95% fluoride F 18	State specific chromatography procedure SOP#_____	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 SOP# _____	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	State limit and provide justification (Note: the currently approved drug product ahs pH limits of 6.0 – 8.0) Attachment _____ Page_____	pH paper with pH reference standards SOP# _____	Test completed prior to release of drug product
Membrane filter integrity	Specify limit for the filter being used	Bubble point measurement SOP# _____	Test completed prior to release of drug product
Bacterial endotoxins (LAL)	NMT[2] 175 EU/V, in which V is the maximum recommended total dose in mL, at the expiration time. For intrathecal administration, please contact the review division.	State test procedure SOP# _____	Test completed prior to final release of drug product
Sterility testing	Sterile	State test procedure SOP# _____	Test initiated within 24 hours of preparation
Osmolality	Isotonic (specify range)	SOP# _____	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. If residual solvents may be present they should be tested as part of the finished product testing]

9. DESCRIPTION OF ANALYTICAL TEST PROCEDURES

Each standard test procedure is included in the application as identified below:

[Note: Each procedure 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(s) performed (including performance schedule, system suitability standards used, and the acceptance criteria that ensure proper performance of the equipment). Each procedure should be reliable and capable of providing valid data. Where applicable, the procedure should be specific and stability indicating. For chromatographic, spectroscopic (e.g., gamma) and microbiologic procedures, validation data that show suitability of the test procedure for the intended purpose should be included in the attachment where the test procedure is included.]

Test	Test Procedure Number	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			

[Note: Above list of test procedures should correspond to the tests proposed as part of the specifications, and the list may be amended as necessary]

10. MICROBIOLOGICAL VALIDATION

This part describes the information you should submit in Section 10 (microbiological validation) of your NDA/ANDA for PET drug products. At the end of this section, there is a table of contents that you can use to list the information submitted in your NDA/ANDA. Only the indicated information should be should be submitted in this part of the CMC section of your NDA/ANDA and the descriptive guidance provided to assist you need not be included.

The microbiological validation section of the CMC section of your NDA/ANDA 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:

- Production Site. *The production site (name and complete address) should be identified and accompanied by a description of the production 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 this section. 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 CMC*

section of your NDA/ANDA, 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 production 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 NDA/ANDA. 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. Integrity testing by the drug manufacturer is not intended to confirm the filter porosity rating, as is the filter manufacturer's testing. However, in-process 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 or by an alternative filter integrity test method that demonstrates the filter membrane is not torn or detached from the housing. 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. Test methods should be described (or provided by a reference) in your NDA/ANDA. 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 _____°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 sodium fluoride 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 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 production 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 Products is (301) 796-2050.]

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 proposed 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 of 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.