



U.S. Food and Drug Administration

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Submitting Chemistry, Manufacturing and Controls (CMC) Information in an ANDA / NDA for Commonly Used PET Drugs

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PET Drug Content and Format Guidance (Draft)

Guidance

PET Drug Applications — Content and Format for NDAs and ANDAs

- **Fludeoxyglucose F 18 Injection**
- **Ammonia N 13 Injection**
- **Sodium Fluoride F 18 Injection**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078738.pdf>

Content

ANDA

1. Table of contents
2. Basis for ANDA submission (reference to listed drug or approved suitability petition)
3. Patent certification and exclusivity statement
4. Comparison of RLD and generic drug
 - Conditions of use
 - Active and inactive ingredients
 - Route of administration, dosage form, and strength
5. Bioequivalence information
6. Labeling
7. **Chemistry, manufacturing, and controls information**
8. Financial disclosure
9. Debarment certification
10. Field copy certification
11. Other

NDA

1. Index
2. Labeling
3. Summary
4. **Chemistry, manufacturing, and controls information**
5. Clinical pharmacology and toxicology
6. Human pharmacokinetics and bioavailability
7. Clinical data
8. Safety update report
9. Statistical section
10. Case report tabulations
11. Case report forms
12. Pediatric research equity Act (PREA)
13. Patent certification
14. Exclusivity statement
15. Debarment certification
16. Field copy certification
17. User fee cover sheet
18. Financial disclosure form

CMC Sample Formats

- **To facilitate submission of CMC information for commonly used PET drugs – Sample CMC formats are proposed.**
- **Sample formats for CMC are available at:**
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078740.pdf>
- **Sample formats may be used to provide information and data regarding manufacture of commonly used PET drugs.**

CMC – List of Sections

1. Drug product components and quantitative composition
2. Controls for components / raw material
3. Reference standards
4. Production and testing facilities
5. Production of drug substance
6. Production of drug product
7. Container / closure
8. Controls for finished dosage form
9. Description of analytical test procedures
10. Microbiological validation
11. Stability and batch data
12. Vial and outer packaging labels
13. Environmental assessment

Drug Product Components and Quantitative Composition (^{18}F -FDG)

| 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.

Strength

- Expressed in mCi / mL (MBq/mL) at end of synthesis (EOS)
- For ANDA – proposed strength same as the RLD strength.
- Can have higher strength for the multi-dose vial
 - Must submit a suitability petition and have approved suitability petition before ANDA is submitted
 - Can submit a 505 (b)(2) NDA

Controls for Components and Other Raw Materials (^{18}F -FDG)

- **Precursor** (e.g., Mannose triflate) - intermediate and information concerning its manufacture and controls should be included either in the application or may be referenced to a drug master file (DMF) from your supplier, filed with FDA.
 - Name and address of supplier (manufacturer)
 - Specifications
 - COA
 - Acceptance procedures
- **Target** – ^{18}O -Water (starting material)
 - Name and address of the manufacturer (s)
 - Specifications
 - COA
 - Acceptance procedures
 - Recycled?

Controls for Components and Other Raw Materials (^{18}F -FDG)

- **Inactive Ingredients**
 - Name and address of the manufacturer
 - Specifications, representative COA, and acceptance procedures
- **Reagents, Solvents, Gases, Purification Columns, and Other Auxiliary Materials**
 - Name and address of the manufacturer
 - Quality grade (*e.g.*, ACS, USP, etc.) or specifications, representative COA and acceptance procedures
- **Reference Standards (Non-radioactive drug substance and other standards)**
 - Name and address of the manufacturer
 - Specifications, representative COA and acceptance procedures
 - 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 and purity should be submitted in the indicated attachment.

Production and Testing Facilities

For each production and / or testing facility

- **Name and address of the PET drug production facility**
 - The actual production site, not administrative address.
- **Name of the contact person**
- **Phone number, e-mail address**

Production of Drug Substance

- **Batch Formula**
 - Name of each component used in the production of 2-deoxy-2[¹⁸F]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)
- **Production of Radionuclide**
- **Synthesis and Purification of Drug Substance**
 - Radiochemical synthesis and purification equipment
 - Pre-synthesis procedures and verifications
 - Radiochemical synthesis and purification operation
 - In-process controls
 - Post synthesis procedures
 - Cleaning, etc.

Radiochemical Synthesis and Purification Equipment

- Manufacturers of automated equipment may submit Type V DMF
 - Equipment description and principle of operation
 - Equipment specifications
 - Quality system information
 - Design controls
 - Performance standards essential requirements
 - Design verification testing including programming logic / software testing
 - Safety margin testing
 - Equipment shelf-life
 - Risk assessment including failure mode, effects, and criticality analysis (FMECA)
 - Functional and electrical testing
 - Bench testing, including extraneous environment testing
 - Data for performance verification studies
 - Results of USP extractable study per chapter <381> and USP biological reactivity as per chapter <87> and chapter <88> on elastomeric components that come in contact with the drug

Production of PET Drug Product

- **Production Operation**
 - Formulation procedure
- **Reprocessing of PET Drug Product**
 - e.g., Re-filtering the final product if membrane filter integrity test fails
- **Packaging and Labeling**

Container Closure System

- **Supplier of Container Closure System**
 - Specifications
 - Acceptance procedures
 - Certificate of analyses (COA)
 - DMF reference (sterility assurance)- LOA
- **Specification for Glass Vial**
 - Dimension drawings, type of glass (e.g., USP type I)
- **Specifications for Elastomeric Stoppers**
 - Dimension drawings
 - DMF reference with LOA
- **Specifications for Aluminum Crimp Seal**
 - Dimension drawings

Controls for Finished Dosage Form

- **Finished product must meet specifications (meet acceptance criteria when tested according to the submitted procedure) throughout shelf-life.**
- **Test performed prior to final release of the batch**
 - Appearance (color and clarity),
 - Radiochemical identity
 - Radiochemical purity
 - Radionuclidic identity (half-life)
 - pH
 - Assay
 - Impurities (as appropriate)
 - Radiochemical
 - Chemical (e.g., kryptofix, other chemical impurities, total impurities)
 - Residual solvents
 - Specific activity (as appropriate)
 - Membrane filter integrity
 - Bacterial endotoxins
 - Stabilizer (antioxidant) assay (if present)

Controls for Finished Dosage Form

- **Test performed subsequent to final release of a batch**
 - Sterility

- **Periodic quality indicator tests (PQIT)**
 - Radionuclidic purity (on decayed sample using a high-sensitivity detector)
 - Class III residual solvents (e.g., ethanol)
 - Other justified tests.

Other Tests

Osmolality:

When the tonicity of a product is declared in its labeling, appropriate control of its osmolality should be performed. Data generated during development and validation may be sufficient to justify performance of this procedure as an in-process control or direct calculation of this attribute or other controls during the manufacturing process.

Analytical Procedures

- **For Analytical Procedures**
 - The analytical supplies and their quality used
 - The equipment and the settings used during the performance of the procedure
 - The preparation of test, standard, and analytical solutions
 - The system suitability test(s) performed (including system suitability standards used, and the acceptance criteria that ensure proper performance of the equipment)
 - Detailed description of the test procedure
 - Exact calculations performed in quantitative procedures
 - The recording of the results

Analytical Method - Validation

- A compendial method, generally, does not need to be validated. However, you will need to show (verify) that the method is suitable for your production and analytical equipment and system used.
- Validation / Verification for
 - Chromatographic methods including different equipment used at different sites
 - pH method (suitability of pH paper in relation to the pH meter)
 - Impurity limit methods (e.g., Cryptand 222 method, at proposed limit, is capable of distinguishing concentrations that are higher and lower than the limit concentrations)
 - Bacterial endotoxin method
 - Sterility method

Stability / Batch Data

- Expiration dating period (time) from EOS calibration time
- Release and stability data on three batches produced at the upper range of the proposed strength (radio-concentration)
- Batch stored in same container closure system as proposed for commercial product
- Vial stored in inverted position
- All tests performed at release
- Tests for appearance, radiochemical purity, impurities (chemical and radiochemical degradation), pH, and assay should be assessed for stability
- Post-approval stability protocol

Labels

- **Vial (container) label**
- **Lead shield (carton) label**
- **Can be in module 1 of the application (if CTD format is submitted)**

Environmental Assessment

^{18}F -FDG

In accordance with 21 CFR 25.31(b), the [*insert name of applicant*] 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 [*insert name of applicant* 's] knowledge, no extraordinary circumstances exist.



Thank You!