



Content and Format of Chemistry, Manufacturing, and Controls (CMC) in a New Drug Application (NDA) -PET Drug Products-

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Outline

- Overview of NDA Content and Format
- General Requirement for Providing CMC Information.
- Resources for NDA
- Resources for CMC
- CMC Section Comments



NDA Content and Format

- Cover Letter
- Application Form – 356h
 - list of items on page 2 of form FDA 356h
 - *Index*
 - *Labeling*
 - *Summary*
 - *Chemistry*
 - *Clinical pharmacology and toxicology*
 - *Human pharmacokinetics and bioavailability*
 - *Clinical data*
 - *Safety update report*
 - *Statistical section*
 - *Case report tabulations*
 - *Case report forms*
 - *Patent Certification and Exclusivity Statement*
 - *Establishment description*
 - *Debarment Certification*
 - *Field copy certification*
 - *User fee cover sheet (Form FDA 3397)*
 - *Financial Information*
 - *Other*



PET NDA and ANDA Guidance (Draft)

- FDA has issued draft guidance, “PET drug Applications – Content and Format for NDAs and ANDAs”.
- Draft guidance website:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078738.pdf>
- Provides information to assist in preparing NDAs and ANDAs for certain PET drugs (Fludeoxyglucose F 18 injection, Sodium fluoride F 18 injection and Ammonia N 13 injection).



Types of NDAs

- 505(b)(1) – studies submitted are performed by the applicant.
- 505(b)(2) - rely for approval on references to studies conducted by others and/or on published literature.
- Applicants submitting 505(b)(2) NDAs for **Certain PET drugs** can rely on the FDA's review of the literature as described in the PET Safety and Effectiveness Notice (65 FR, 12999) and/or on previous approvals of PET drugs for certain indications.
- An application can have multiple manufacturing sites that produce the same PET drug product.



Requirement for CMC

- Required under Section 505 (b). [21 USC §355]
- Submission required as per 21 CFR 314.50 – Content and format of an application.



Content and Format of NDAs

- Current preferred format for submitting an application, including CMC is the Common Technical Document (CTD)
 - Paper CTD or
 - electronic CTD (e-CTD) format
- The items cited in the PET NDA / ANDA draft guidance should be organized in a manner which corresponds to the modules of the CTD as indicated on the Checklist
- Guidance:
 - Submitting Marketing Applications According to the ICH-CTD Format — General Considerations
 - M4Q: The CTD — Quality; M4: The CTD — Quality Questions and Answers/ Location Issues
 - website:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065006.htm>



Drug Substance in NDA - CTD

- **S.1 General Information: Nomenclature, Structure, General Properties**
- **S.2 Manufacture**
 - **Manufacturers**
 - **Description of Manufacturing Process and Process Controls**
 - Flow diagram
 - Process Narrative
 - Process Controls
 - **Control of Materials**
 - Starting Materials
 - Reagents, Solvents, Auxiliary Materials
 - **Control of Critical Steps and Intermediates**
 - **Manufacturing Process Development**
- **S.3 Characterization**
 - **Elucidation of Structure**
 - **Other Characteristics**
 - Physicochemical properties
 - Solid State Forms
 - **Impurities**
 - Types (organic, inorganic, residual solvents)
 - Classification (specified/unspecified, identified/unidentified)
 - Reporting, Identification and Qualification Thresholds
 - Acceptance Criteria
 - Qualification
- **S.4 Control of the Drug Substance**
 - Specifications
 - Analytical Procedures
 - Validation of Analytical Procedures
 - Batch Analyses
 - Justification for Specifications
- **S.5 Reference Standards**
- **S.6 Container Closure System**
- **S.7 Stability**
 - Stability Protocol and Data Evaluation
 - Forced Degradation/Stress Testing
 - Photostability
 - Stability Summary and Conclusion
 - Post-approval Stability Protocol and Commitment
 - Stability Data



Drug Product in NDA - CTD

- **Drug Product**
- **P.1 Description and Composition**
- **P.2 Pharmaceutical Development**
 - Drug Substance
 - Excipients
 - Formulation Development
 - Manufacturing Process Development
 - Container Closure Suitability
- **P.3 Manufacture**
 - Manufacturer
 - Batch Formula
 - Description of Manufacturing Process and Process Controls
 - Control of Critical Steps and Intermediates
- **P.4 Control of Excipients**
- **P.5 Control of the Drug Product**
 - Specifications (release, stability, in-house)
 - Analytical Procedures
 - Validation of Analytical Procedures
 - Batch Analyses
 - Justification of Specifications
- **P.6 Reference Standards**
- **P.8 Stability**
- **P.7 Container Closure Systems**
 - Primary, Secondary, Functional and Non-Functional Secondary Packaging
 - Stability Protocol and Data Evaluation
 - Forced Degradation/Stress Testing
 - Photostability
 - Stability Summary and Conclusion
 - Post-approval Stability Protocol and Commitment
 - Stability Data
- **Regional Information**
- **Executed Batch Records**
- **Comparability Protocols**
- **Method Validation Package**
- **Module 2 of CTD**
 - Quality Overall Summary



Drug Master Files

- A DMF contains information about a drug substance, a component, or a container/closure system that is proprietary (i.e., belongs to someone else)
 - Type II - Drug substance, drug substance intermediate, and materials used in their preparation, or drug product
 - Type III - Packaging materials
 - Type IV - Excipient, colorant, flavor, essence, or materials used in their preparation
 - Type V - FDA accepted reference information



Drug Master Files

- The information may not be available to you, but you may need it as part of your NDA, ANDA.
- The chemistry section of Form FDA 356h may ask you to provide this information.
- This information is usually available from the supplier or manufacturer of the subject of the DMF.
- Rather than providing the information directly to you, the manufacturer may choose to *hold a DMF*. The DMF holder provides the information directly to the FDA (submits DMF to FDA).



DMF Reference

- If a manufacturer holds a DMF that you would like to reference, you should ask them to provide you with a letter of authorization (LOA), which you must include with (and reference in) your application and list on your Form 356h.
- LOA from the DMF holder grants the FDA authorization to refer to information in their DMF during the review of your NDA, ANDA or IND.



Drug Master Files (DMF) Resources

- The regulatory requirements for a DMF-21 CFR 314.420
- Guidance:
 - Guideline for Drug Master Files
 - <http://www.fda.gov/cder/guidance/dmf.htm>
- Current DMF submission address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266



NDA RESOURCES

- NDA
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm>
 - Guidance documents providing Agency's current thinking on a particular subject
 - Laws, Regulations, Policies and Procedures
 - Prescription Drug User Fee Act (PDUFA) related documents
 - NDA Forms and Electronic Submissions
 - Other useful information links



CMC RESOURCES

- CMC Guidance:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm>
- CMC Microbiology Guidance:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064983.htm>



Drug Substance Description & Characterization

- Chemical name, USAN name, Molecular formula, Molecular weight, etc.
- Source (synthetic, animal, plant, biotechnology-derived).
- General properties
 - Non-radioactive portion
 - Radionuclide (e.g., such as type of radioactive emission, abundance and energy, radioactive half-life, nuclear reaction, etc.)
- Specific activity
- Impurities
 - radionuclidic, radiochemical or chemical (organic, inorganic, other)
- Physical properties (can be determined using non-radioactive standard)
 - (e.g., solubility, partition coefficient, ionic charge, dissociation constants, etc.)
- Evidence to support proposed chemical structure, including stereochemistry.
 - Use same lot of reference standards for characterization.



Drug Substance

- Since the radioactive drug substance is prepared in situ during the production of the drug product, the drug substance section should also CMC information for non-radioactive intermediate (precursor) from the first starting materials.
 - The information may be provided in a type II DMF or the NDA.
- Specifications for the non-radioactive intermediate (precursor) and radionuclide (if obtained from a vendor) should be included.
 - Specifications should include acceptance criteria for identity, assay, and impurities, and other appropriate quality attributes (e.g., water content).
 - A description of the test methods.
 - Analytical data (e.g., IR / NMR / MS / UV spectrum, etc. and their interpretation to prove the identity, and HPLC chromatograms to support the purity level and impurities profile) material:
 - Representative batch data and / or a copy of the certificate of analysis should also be submitted.
 - Data on precursor reference standard lot (if used).

Stability

- Drug Substance Section
 - In this section also include:
 - A brief description of the stability of the non-radioactive intermediate (precursor).
 - Also describe the container closure and the storage conditions.
- Drug Product Section:
 - Description of the stability study and the test methods used to monitor the stability of the drug product.
 - The drug product should be assessed for stability - both radiolysis and chemical degradation (e.g. pH dependant).
 - Where there is to be a range of radioactivity stability should be assessed at the upper limit.
 - Stability studies should be performed in the container closure in which the drug product will be stored.

PET Drug Synthesizers

- Recommend Type V Drug Master File for PET Drug Synthesizers:
 - Equipment description and principle of operation
 - Equipment specifications
 - Quality system information
 - Design Controls
 - Essential performance standards requirements
 - Design verification testing including programming logic / software testing
 - Safety margin testing
 - Equipment shelf-life
 - Risk assessment including FMECA
 - Functional and electrical testing
 - Bench testing including extraneous environment testing.
 - Data for performance verification studies.



Drug Product Specifications

- Establish specifications for each PET drug product
 - Critical quality attributes (CQA) that are indicative of product's safety and effectiveness
- Before final release, conduct an appropriate laboratory determination to ensure that each batch of a PET drug product conforms to specifications, except for sterility
 - Sterility is assured by process monitoring and controls, and confirmed by end product testing (sterility test should be started within 30 hours of end of production)



Drug Product

- Appropriate laboratory determination could involve
 - Finished product testing of each batch
 - In-process testing of an attribute that is equivalent to the finished-product testing of that attribute
 - Continuous process monitoring of one or more attributes with statistical process controls
 - QbD, PAT
 - Some combination of the above approaches
- Approach should be set forth in the product's marketing application (NDA or ANDA)



Non-Critical Quality Attributes

- Some product attributes may not be critical to the safety or efficacy of the product, but nevertheless are important in assessing the ongoing quality of the product and to assure that the manufacturing process is in control
 - Radionuclidic purity (sometimes)
 - Certain class 3 residual solvents
- When justified, these could be tested as periodic quality indicator tests (PQIT)
 - Performed at predetermined intervals rather than on a batch-to-batch basis
 - Included in product's marketing application - **listed separately from the specification**
 - Established and refined under firm's internal quality system



Conclusion

- NDA Content and Format
- General Requirement / guidance for Providing CMC information.
- Resources for NDA
- Resources for CMC

THANK – YOU!