Drug Substance Review Process in ANDAs

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Outline

- Regulatory Basis
- Submission Type and Format
- Technical Content
- References

Regulatory Basis

Chemistry, manufacturing, and controls (CMC) information must be submitted to support the approval of an abbreviated new drug application (ANDA).

21 CFR 314.94 (a)(9);
505(j)(4)(A) of the Federal Food, Drug, and Cosmetic Act (the Act).

Submission Type

- ANDA Module 3S
- Type II Drug Master Files (DMF)

Format

- eCTD
- May 15, 2017
- Drug Substance info in Type II DMF

S.1 General Properties

S.1 Nomenclature, Structure and General Properties

- General description (appearance, color, physical state)
- Solubility (aqueous solubility and relevant organic solvents)
- Melting point
- Partition coefficient (octanol/water)
- Polymorphic form
- Stereochemistry
- Specific optical rotation
- Particle size
- Hygroscopicity
- Dissociation constant
- pKa, Solution pH

S.2 Manufacture

S.2.1 Manufacturers

- API Manufacturers (including alternates)
- Facilities proposed to do routine commercial release/stability testing of the drug substance (including alternates)
- Facilities that micronize the API
- For Animal/Plant-Derived Products, the facilities that perform crude extraction prior to purification of API (including alternates)
- Sites that directly sterilize the API
- Provide the name, address, contact person, and responsibility of the site or facility
- FEI and DUNS numbers
- Current Good manufacturing practices (cGMP) statement for each DS manufacturing and release/stability testing sites

S.2 Manufacture (Cont)

S.2.2 Description of Manufacturing Process And Process Controls

- Stage by stage synthetic scheme
- Clearly indicates the regulatory SM as well as isolated intermediates
- Scheme should include reagents, solvents, reaction conditions and any other critical reaction parameters
- Brief manufacturing process and process flow chart for each stage of the process
- Detailed description of the manufacturing process
- Quantity of input materials, in-process tests
- Expected yield range and actual yield for each stage of the process (weight/mole %)
- Flow chart showing entry and exit of materials, in process tests

S.2 Manufacture (Cont)

S.2.3 Control of Materials

Starting Material

- Specifications and Standard test procedure (STP)
- Specifications should include at least these tests: specific ID, purity (assay), impurities (single and total)
- Supplier's and in-house COA's
- Route of Synthesis (as applicable) in adequate detail

S.2 Manufacture (Cont)

S.2.4 Controls of Critical Steps and Intermediates

- Per ICH Q11, control of critical quality attributes (CQAs) of DS:
  - By specification of final drug substance
  - By upstream controls such as in process testing and intermediate isolation
- Summary table of in process Controls (IPCs), table of critical process parameters (CPPs)
- For control of impurities, it is important to understand the formation, fate and purge of impurities, as well as their relationship to the resulting impurities that end up in the drug substance as CQAs.

S.2 Manufacture (Cont)

S.2.5 Process Validation and/or Evaluation

- Process validation is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a drug substance or intermediate meeting its predetermined specifications and quality attributes (ICH Q7).

S.2.6 Manufacturing Process Development

- Validation summary including batch description with traceability, and analytical data of SMs, intermediates, in-process test results and final API.
- Sterile process validation will be evaluated by Division of Microbiology.
- Provide a summary of the process development report to support starting material selection, process design, optimization and scale up, and control strategy in place.

S.3 Characterization

- Characterization studies: IR, UV, NMR (1D, 2D), Elemental Analysis, Mass spectrometry, X-ray diffraction (XRD)
- Original spectra and interpretation of data:
  - Peak assignment tables for IR, chemical shift values and assignments for NMR, fragmentation pattern in MS, elemental analysis results
- Demonstration of proper isomeric structure:
  - Enantiomers/diastereomers/alkene stereoisomeric compounds,
  - discussion regarding the risk of epimerization/racemization during the synthetic process and storage
- Polymorph consistency (if applicable)
- Comparison with authenticated material (USP or Ph. Eur. Ref Standards, extracted DS from RLD)
- Literature references supporting proposed structure (e.g. NMR, IR, optical rotation, especially when compared to other isomeric or pXRD data for various polymorphic forms)

S.4 Control of Drug Substance

S.4.1 Specification

- A Specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described (ICH 6A).
- It establishes the set of criteria to which a new drug substance or drug product should conform to be considered acceptable for its intended use.
- The tests included are part of the strategy to control & ensure DS quality. They are proposed and justified by the DS manufacturer.

S.4 Control of Drug Substance

S.4.2 Analytical Procedures

S.4.3 Validation of Analytical Procedures

- Analytical procedure is a method used to insure the identity, strength, quality, purity, and potency of DS.
- Method Validation is a process of demonstrating that the analytical procedure is suitable for their intended use.
- Stability-Indicating method is a validated analytical procedure that can detect the changes with time in the pertinent properties of DS.

S.4 Control of Drug Substance

S.4.4 Batch Analyses

- CoAs of validation batches in this section
- CoA of micronized/non-micronized batch, recovered solvent or reprocessed batch
- CoA with updated specification
- Results should meet the specification limits

S.4.5 Justification of Specification

- USP monograph or other compendia
- ICH guidelines
- Development batches
- Toxicological data
- Literature

S.5 Reference Standards

- A substance prepared for use as the standard in an assay, identification or purity test. It has a quality appropriate to its use (ICH Q6A)
- Used in the analytical methods and critical in validating specificity of an identity test
- This section needs to contain a description of how primary and secondary (working) reference standards are qualified
- Compendial Primary RS : lot #; no characterization required
  - If firm is using in-house secondary WS as well then full characterization may be provided or at minimum an IR spectra comparison to the USP RS, COA and expiry/Retest date stated for qualification
- In-house Primary RS:
  - origin batch and lot #
  - full characterization data (data in 3.2.S.3.1 provided may be referenced)
- COA
- Expiry/retest date

S.6 Container Closure System

- Detailed description of the primary, functional components, and secondary packaging
- Clearly identify materials of construction; IR needed for polybags
- Provide name of manufacturer/supplier for primary packaging
- Provide specifications for each component
- Provide representative vendor or in-house COA's for primary packaging
- Documentation showing primary packing compliance with 21 CFR (174-186) (food safety statement) for each vendor
- Detailed discussion of functional aspects of the CCS to ensure product quality during shipping and storage for sensitive drug substances (i.e., hygroscopic, light or air sensitive, etc.).

S.7 Stability

- Provide the stability protocol
- Testing specifications, conditions and time points
- List the tests and acceptance criteria used during stability and retest
- Identify which tests will performed at each time point (some tests like microbial testing may only be done at certain time points and this should be clearly indicated)

S.7 Stability (Cont'd)

- Provide a description of container closure system used during stability (should match the system described in S.6)
- Provide analysis of the stability data with explanations of any trends
- Explain how this data supports the retest/expiry period (ICH Q1E)
- Clearly state the retest date
- Provide a summary of root cause analysis reports for any out of specification (OOS) results

Information Sources

- DMF Web site–Contains current list of DMFs, links to supporting guidances and advice for DMF holders not in DMF Guidance (1989) http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm
- DMF Guidance link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073164.htm
- DMF questions:
  - General (Administrative) Questions: dmfquestion@fda.hhs.gov
  - GDUFA specific: DMFOGD@fda.hhs.gov
  - Technical questions e.g. about amount of stability data needed, designation of compound as a starting material: cder-opq inquiries@fda.hhs.gov
- Electronic submissions: esub@fda.hhs.gov

Thank you for your attention!

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