Common Deficiencies in Drug Master Files (DMFs)

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Mission

The Office of Pharmaceutical Quality assures that quality medicines are available to the American public

Vision

The Office of Pharmaceutical Quality will be a global benchmark for regulation of pharmaceutical quality

Slogan

'One Quality Voice'

Objective

- General Considerations regarding Type-II DMFs
- CTD Format
- Briefly touch on the contents and common deficiencies in each section of the drug substance module
- Brief summary
- Challenge questions

Type-II DMFs: General Considerations

- Type II drug master files (DMFs): Chemistry Manufacturing and Control (CMC) of the active ingredient of a drug product
- Absence of adequate information
  - ➢ fail completeness assessment
  - ➢ delay in the DMF becoming adequate
  - ➢ delay in the ANDA approval
- Understanding of the critical chemistry and manufacturing parameters needed to ensure consistent production of high-quality APIs
- Provide high quality submissions
- *A request:* It would be extremely helpful for applicants to submit a 3938 form with their DMF submissions.

CTD Format

S Drug Substance Modules

- S.1 General Properties
- S.2 Manufacture
- S.3 Characterization
- S.4 Specification
- S.5 Reference Standard
- S.6 Container Closure System
- S.7 Stability

S.1 General Information

- **S.1.1 Nomenclature**

  International Nonproprietary Name (INN), Compendial name (if applicable), Chemical names, other generic name, proprietary names, Chemical Abstract Service (CAS) registry number

- **S.1.2 Structure**

  Structure including stereochemistry (if applicable), molecular formula, molecular weight

- **S.1.3 General Properties**

  Physicochemical Properties and Other relevant properties (e.g., physical description, pKa, polymorphism, solubility characteristics, hygroscopicity, melting point, chirality, isomerism, etc.)

S.1 Deficiencies

- Commonly observed missing information:
  - polymorphic characterization
  - hygroscopicity studies
  - Solubility (especially solvents used in the manufacturing process)
  - stereochemical and chirality information
- Failure to provide explanation for leaving out a property
- Inconsistency with information in scientific literature (make full use of scientific literature!)

S.2 Manufacture

- S.2.1 Manufacturer
- S.2.2 Description of Manufacturing Process
- S.2.3 Control of Material
- S.2.4 Control of Critical Steps and Intermediates
- S.2.5 Process Validation and/or Evaluation
- S.2.6 Manufacturing Process Development

S.2 Deficiencies

- Failure to provide information of any/additional contractors involved in manufacturing and release testing of the drug substance (e.g., name, address, FEI#, responsibility)
- Failure to provide description of post processing procedures such as micronization (i.e., how is it performed; equipment used)
- Incomplete synthetic schemes (e.g., reagents, catalysts, solvents, reaction conditions, intermediates, bracketing non-isolated intermediates etc.)
- Incomplete description of the manufacturing process (e.g., batch size, input size, theoretical & expected yields etc.)

S.2 Deficiencies cont'd.

- Lack of adequate justification for starting material designation
- Missing information for intermediate:
  - full name and address of the manufacturing site and contact Info.
  - complete manufacturing information
  - statement on Class I solvents
  - controls of impurities and residual solvents in the specification
  - vendor and in-house COAs
  - commitment that if vendor for the intermediate is changed/added or the process of manufacturing is modified in any way, the agency as well as the ANDA holders will be informed of the changes

References: ICH Q 7A; Scott, B. Pharm. Tech. 36 (1), P. 63-66; ICH Q11, Sections 5.1.1 and 5.2.1

S.2 Deficiencies cont'd.

- Frequently missed-out information
  - reprocessing procedures
  - solvent recovery process
  - critical process parameters/ material attributes
  - complete COAs for all intermediates, if isolated
- Absence of a process validation and/or evaluation summary
  - batch sizes, yield data, and analysis results

S.3 Characterization

- S.3.1 Elucidation of structure and other characteristics
- S.3.2 Impurities

S.3 Deficiencies

- Incomplete characterization data including interpretation of spectral data for API
- Failure to address stereo-chemical features (e.g., chiral HPLC, specific optical rotation, single crystal XRD etc.)
- Missing information on polymorphic characterization (e.g., PXRD, DSC, FTIR, etc.)
- Poor presentation of data
    - illegible copies
    - missing comparison, expansion etc.

S.3 Deficiencies Cont'd.

Missing impurity information:

- Failure to provide complete Hazard Assessment* summary of all potential and actual impurities in the S.3.2 Impurities subsection.
- Missing residual solvents, inorganic impurities
- identification of impurities including IUPAC names and chemical structures
- Classification as process related and/or degradation products
- Safety studies

*Reference: ICH M7(R2) and ICH M7(R2) Q&A

S.3 Deficiencies Cont'd.

Missing impurity information:

- Failure to provide complete Nitrosamine Risk Assessment in S.3.2 Impurities subsection.
  - Identifying and controlling all potential nitrosamine and Nitrosamine Drug Substance Related Impurities (NDSRIs) in the manufacturing process as described in the Recommended Acceptable Intake Limits for Nitrosamine Drug Substance Related Impurities (NDSRIs) and the Control of Nitrosamine Impurities in Human Drugs Guidances for Industry

S.4 Control of Drug Substance

- S.4.1 Specification
- S.4.2 Analytical Methods
- S.4.3 Validation of Analytical Methods
- S.4.4. Batch Analysis
- S.4.5 Justification of Specification

S.4 Deficiencies

- Incomplete Specifications
  - agreement with USP monographs and ICH Q3A(R2)
  - other compendia (EP, BP, or JP)
  - unidentified and unspecified impurities at recommended ICH Q3A (R2) levels
  - residual solvents levels (ICH Q3C, USP <467> etc.)
  - residual metals (USP <231>, <232>)
  - quantitative and qualitative counterion tests

S.4 Deficiencies Cont'd.

- Lack of identification test for counter ion [quantitative test may be requested if the counter ion is changed during the synthesis (ICH Q6A)]

- Missing stereo-specific identification test for chiral drug substances (ICH Q6A and CDER Guidance on the development of new stereoisomeric drugs)

- Failure to include USP identification tests as part of drug substance specification

S.4 Deficiencies Cont'd.

- Quantitative results are not reported in actual numerical numbers
- Failure to control potentially mutagenic impurities
  - identification with documentation
  - control per ICH M7(R2) (*Guideline on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk and the ICH M7(R2) Questions and Answers companion document)*
  - higher levels justified based upon Pharmacological/Toxicological studies

S.4 Deficiencies Cont'd.

- Failure to provide equivalency studies between in-house method and USP method
- Failure to demonstrate stability-indicating criteria for Assay and Related substance methods
  - ➢ no or inappropriate stressed conditions
  - ➢ peak purity data
  - ➢ mass balance between assay and related substances results
  - ➢ representative chromatograms (e.g., specificity and sensitivity)

S.4 Deficiencies Cont'd.

- Incomplete Batch analyses data [e.g., batch no., batch size, manufacturing date, manufacturing site (if multiple sites), batch purpose (e.g., validation, stability) etc.]

- Failure to provide justification for specification – may be based on following but not limited to:
  - Development data, ICH guidance, batch analysis data, toxicology data, stability data, USP or other compendia monograph (EP, BP, JP etc.)

S.5 Reference Standards

Common deficiencies:

- missing lot number of the USP reference standard
- failure to qualify in-house standards against USP reference standard
- missing characterization data for primary standard when there is no USP RS available
- missing qualification data of impurity standards (spectra, COAs, purity, etc.)
- missing identification information of in-house impurity standards (e.g., source, lot number, etc.)

S.6 Container Closure System

Common deficiencies:

- failure to provide a certificate for the bag that is in contact with the drug substance (21 CFR 177-186 requirements of Indirect Food Additives Regulation, e.g., 21 CFR 177.1520 for LDPE bags)

- label with insufficient information (e.g., Name of API, Batch No., Storage Conditions, Retest Date, Manufacturer's Name and Address, Date of Manufacture, Net weight, Gross Weight, Caution Statement, etc.)

S.7 Stability

- S.7.1 Stability Summary and Conclusions
- S.7.2 Post-approval Stability Protocols and Stability Commitment
- S.7.3. Stability Data

S.7 Deficiencies

- Failure to provide justification for stability specification (some tests may be excluded in stability specification if justified)
- Failure to support retest date/ expiration date by stability data
- Missing explanation for out-of-specification results:
  - summary of investigation
  - supporting analytical report
  - measures to address the issue

Summary

- Some sections generate more deficiencies (e.g., impurity control, manufacture)
- Understand the critical chemistry and manufacturing parameters
- Use regulations, development data and good science to justify the choices
- Make use of scientific literature

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