Drug Substance Information

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Two Quality Sections in CTD

- **CMC information is provided in two distinct sections in CTD**
- **Section 2.3**
  - Quality Overall Summary
- **Module 3**
  - 3.2.S for Drug Substance
  - 3.2.P Drug Product

Global CMC Considerations

- Chemistry Manufacturing and Control data recommendations are outlined in *ICH MQ4*, Quality Guidance by ICH
- Actual data and documentation requirements vary from market to market
- Information and data to be provided are often greatly impacted by compendial requirements
- Clear understanding of stability requirements such as storage conditions, and minimum data for filing is a huge time-saver
- Scientific Data is mapped into different CTD sections in 32s and 32p Modules

Mapping Module 3 Quality Sections

What is CTD Mapping?

- Each and every quality section in CTD is a summary technical report
- Different functional areas within a plant generate these technical reports
- Technical reports contain data which may not be written in a standard format
- Data from technical reports is written in a standard format that becomes a CTD section
- In short, CTD mapping is understanding what technical report supports what quality section in CTD

Typical Examples of Technical Reports

- Characterization
- Formulation Development
- Manufacturing Development
- Method Validation
- Justification of Specifications
- Process Validation
- Stability Reports
- Stress Studies
- Container-Closure Evaluation

Mapping of DS CTD Sections

Technical reports needed to write CTD sections are provided by functional areas

Section	Title	Functional Area
3.2.S.1	General Information	DS Characterization
3.2.S.2	Manufacture	Manufacturing
3.2.S.3	Characterization	DS Characterization
3.2.S.4	Control of Drug Substance	Analytical
3.2.S.5	Reference Standard	Analytical
3.2.S.6	Container Closure	Manufacturing/packaging
3.2.S.7	Stability	Stability

Mapping of DP CTD Sections

Technical reports needed to write CTD sections are provided by functional areas

Section	Title	Functional Area
3.2.P.1	Description and Composition	Manufacturing
3.2.P.2	Pharmaceutical Development	Manufacturing
3.2.P.3	Manufacture	Manufacturing
3.2.P.4	Control of Excipients	Analytical
3.2.P.5	Control of Drug Product	Analytical
3.2.P.6	Reference Standard	Analytical
3.2.P.7	Container closure	Manufacturing/packaging
3.2.P.8	Stability	Stability

Submission of Drug Substance information-General Notes

- API information in 32s Module is part of the dossier and must be reviewed by the agencies.
- However, in several markets API information can be submitted separately and maintained via a Drug Master File system
- In EU, for a compendial API, one can submit Certificate of EP Suitability (CEP) instead of complete 32S
- In most markets Applicant must provide entire 32S Module in the dossier
- Confidential information, such as Manufacturing process can be submitted to the Agencies directly after discussion and agreement from the Agency

What is Drug Master File? Example in US

- Stand alone submission that is neither approved nor rejected
- Completely closed submission
- A pathway to keep information confidential
- Not a legal requirement
- DMF is reviewed only when referenced by a submitted application IND, NDA, ANDA, 505(b)(2)
- Deficiencies are shared with Holder as well as Sponsor
- Holder is the entity that holds DMF
- Sponsor is the entity who is referencing the DMF
- Five types of DMFS in US

What is Drug Master File? Example in US

Type I	Also knew as site master file that contained facility information. Discontinued now but numbering is retained to avoid confusion
Type II (most common)	Drug substance, Critical intermediate, Drug product Follows ICH-CTD format Submitted in lieu of 32s section in the application
Type III	Packaging material. Discusses components, fabrication, control, toxicity data etc.
Type IV	Novel Excipients.
Type V	Needs prior approval from FDA to submit Used for sterile manufacturing plants and contract facilities for biotech products

Drug Master File systems in other markets

- EU, Australia, Canada, Japan, Singapore, Brazil etc. also have DMF system
- However, the format is different than US.
- For ex, in EU, Canada, Australia DMF is not entirely closed
- API manufacturer chooses to provide only confidential manufacturing section (32s2) also known as Closed Part to the Agency
- Applicant includes other sections in the MAA and these sections are known as Open Part
- Letter of Authorization (LOA) to Reference is required in all these markets.

DS Data-General Information

GENERAL INFORMATION (S.1)

- Nomenclature (S.1.1)
  -Compendial name
  -IUPAC Name
  -Any International Nonproprietary Names
  -Code No., Abbreviations, Nicknames
  -CAS (Chemical Abstracts Service) No.
- Structure (S.1.2)
  -Actual drawing including stereochemistry
  -Molecular formula and Molecular weight

DS Data-General Information

GENERAL INFORMATION (S.1)

- **General Properties (S.1.3)**
  - -Description such as appearance, color, physical state
  - -Melting or boiling point
  - -pH of the solution
  - -Solubility profile (aqueous and non aqueous, as applicable)
  - -Hygroscopicity
  - -Optical rotation (if applicable)
  - -Partition coefficient
  - -dissociation constants
  - -Physical forms such as polymorph, solvate, hydrate

DS Data-Manufactures

MANUFACTURE (S.2)

- Manufacturers (S.2.1)

  -Name, address and function of all site (s) involved

  -Building numbers, sterile processing room numbers

  -Establishment registration number (for ex. US, Canada submission)

DS Data-Description of Manufacturing Process

MANUFACTURE (S.2) **CONFIDENTIAL INFORMATION FOR EU STYLE DMF**

- **Description of Manufacturing Process and Process Controls (S.2.2)**
  - Synthesis Route showing all molecular transformations, reagents, solvents, catalysts etc
  - Flow diagram depicting materials going in and coming out, in-process controls, typical yields, operating parameters such as temperature, time and pH ranges
  - Narrative description with more details than flow chart including analytical methods for in-process controls
  - Process Controls
  - Reprocessing, Reworking, Recovery, Regeneration if applicable

DS Data-Control of Raw Materials

MANUFACTURE (S.2) **CONFIDENTIAL INFORMATION FOR EU STYLE DMF**

- Control of Materials (S.2.3)
  - Starting material(s),reagents, solvents, catalysts, processing aids, etc.
  - Specification
  - Test methods

DS Data-Control of Critical Steps and Intermediates

MANUFACTURE (S.2) CONFIDENTIAL INFORMATION FOR EU STYLE DMF

- **Controls of Critical Steps and Intermediates (S.2.4)**
  - All critical operating parameters (temperatures, time ranges, pH etc)
  - Environmental controls (humidity)
  - In-process tests
  - All tests performed on intermediates, post-synthesis materials, unfinished drug substance
  - Numeric ranges, limits, or acceptance criteria for each of the above control

DS Data-Process Validation

MANUFACTURE (S.2) CONFIDENTIAL INFORMATION FOR EU STYLE DMF

- **Process Validation and/or Evaluation (S.2.5)**
  - All manufacturing processes should be validated
  - Process validation demonstrates consistency as well as control over the manufacturing of drug substance
  - Complete manufacturing data (batch record) of three consecutive batches under a protocol approved by Quality department
  - Some Agencies require just process validation protocol be included in a dossier while some agencies require a complete report

DS Data-Process Development

- **MANUFACTURE (S.2)** **CONFIDENTIAL INFORMATIONCONFIDENTIAL INFORMATION**
- **Manufacturing Process Development (S.2.6)**
  - A comprehensive and historical review of manufacturing process development

DS Data-Structure Elucidation

- **Characterization (S.3)**
  - **Elucidation of Structure and other Data (S.3.1)**
  - Spectral data such as NMR, Mass, IR, UV, X-ray and elemental data
  - Physicochemical Characterization data to support information provided in S.1.3, General Properties

DS Data-Impurities

- **Characterization (S.3)**
  - **Impurities (S.3.2)**
  - List of actual and potential organic, inorganic impurities and residual solvents
  - List of degradation products observed during the stress studies
  - Impurities are required to be reported, and/or identified and/or qualified per threshold recommendation by the ICH guideline Q3A.
  - The methods used for identification are listed in this section as well
  - Analytical methods used for detecting impurities
  - Synthesis route in case impurities are independently synthesized

What is stress studies?

- Drug substance is subjected to extreme harsh degradation conditions till it yields degradants
  - Thermal degradation
  - pH degradation
  - Oxidative degradation
  - Photo-degradation
- To establish degradation pathways of drug substance
- To reveal the structure of degradation products and synthesize them for qualification studies, if needed
- To determine the intrinsic stability of a drug substance that will be helpful in formulation selection
- To develop stability indicating analytical methods

DS Data-Specification

- **Control of Drug Substance (S.4)**
- **A separate, S4 modules from DP manufacturer is required if API is supplied by a third party. A very common scenario for generic dossiers.**
  - Specification (S.4.1)
    - Must establish Identity, Strength, Quality and Purity
    - Combination of analytical tests and acceptance criteria
    - Established per recommendation of ICH Q6A, relevant compendia, historical batch analysis data etc.
    - Combination of universal tests (identity, strength, quality and purity) and specific tests that are critical for the performance and intended use the dosage form
    - Ex. Particle size is very critical for solid oral dosage
    - Chiral purity is critical if a single enantiomer is API
    - DP manufacturer submits a separate 3s41 module indicating the acceptance criteria, it has established for the Drug Substance.

DS Data-Analytical Procedures

- **Control of Drug Substance (S.4) continued**
  - Analytical Procedures (S.4.2)
    - Combination of in-house and compendial
    - Typically, in house methods are described fully
    - Some Agencies require a complete description of all methods regardless
    - If the DP manufacturer is performing any additional test then those tests should be described in a separate 3s42 section.

DS Data-Validation of Analytical Procedures

- **Control of Drug Substance (S.4)-continued**
  - Validation of Analytical Procedures (S.4.3)
    - All non compendial (in house) analytical methods should be validated as described in ICH guideline Q2A
    - It's a scientific demonstration that method is fit for its purpose
    - If the DP manufacturer is performing any additional methods that are in-house then those methods need to be validated and provided in a separate 32s43 module

DS Data-Batch Analysis

- **Control of Drug Substance (S.4) -continued**
  - Batch Analysis (S.4.4)
  - Demonstrates consistency of the manufacturing process and compliance with predetermined specification
  - All release results are tabulated and supported by actual copies of Certificates of Analysis
    - Several agencies require original COAs with wet signature
    - Several agencies mandate at least one batch should be recentely manufactured
    - DP manufacturer should provide its COAs showing DS is acceptable

DS Data-Justification of Specification

- **Control of Drug Substance (S.4)-continued**
  - Justification of Specification (S.4.5)
    - Tests and acceptance criteria, both should be justified
    - Justification for the proposed drug substance specifications should be based on
      - ICH Q6A (intended use, dosage form etc.)
      - Relevant historical developmental data (S.2.6)
      - Information on impurities (S.3.2)
      - Standards in an official compendium
      - Batch analyses data (S.4.1)
      - Stability studies (S.7)
      - Toxicology data, and any other relevant data

DS Data-Reference Standard

- **Reference Standard (S.5)**
  - Reference standards are prepared for DS as well as impurities
    - Identify the source (official source such as Ph. Eur., USP or in house)
    - Provide characterization data if source is in-house
    - Provide Certificate of Analysis regardless

DS Data-Container Closure

- **Container Closure (S.6)**
  - Include following information for primary packaging
    - Material of construction
    - Relevant specification for ex. thickness of a polyethylene bag
    - Some agencies require to include drawings, suppliers chemical tests and acceptance criteria
  - Justify choice of primary packaging
    - Compatibility (non reactive material)
    - Protection from moisture, light etc
  - Some Agencies require a compliance certificate

DS Data-Stability Summary and Conclusions

- **Stability (S.7)**
  - Stability Summary and Conclusions (S.7.1)
    - Performance of API in terms of storage
    - Results and conclusion of Forced degradation study under stress conditions, such as light, temperature, heat, humidity, acid basic and oxidation hydrolysis are included
    - stability design (batch numbers, date of manufacturing, scale etc.)
    - Typically 3 batches of DS are evaluated for stability at long term storage conditions as well as 6M accelerated conditions
    - Conclusion regarding labeled storage conditions and retest period/expiration dating is based on these results

DS Data-Post Approval Stability Protocol and Commitment

- **Stability (S.7)**
  - Post Approval Stability Protocol and Commitment (S.7.2)
    - Summarize post approval study design if different than the one provided in S.7.1
    - Provide commitment regarding any ongoing or incomplete stability study

DS Data-Stability Data

- **Stability (S.7)**
  - Stability Data (S.7.3)
    - Tables depicting actual stability
    - Each parameter is tracked over the period and numeric values indicate stability
    - Signed and reviewed by QA

Questions

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