Drug Product

Kalpana Nimkar, Ph.D.

Associate Director, Global Regulatory Affairs

Hospira, a Pfizer Company

DP Data-Description and Composition

- **DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT (P.1)**
  - Description of Dosage Form
    - A short statement about the product and its dosage form, strengths
  - Container Closure System
    - Type of container closure (vial, bottle, blister)
    - Material of construction ex. Ex. Daikyo CZ Resin Vial with West Stopper Teflon 2 coated, 20mm Seal

DP Data-Composition Statement

- **DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT (P.1)**
  - Composition Table for each strengths and presentations
    - Include a table of qualitative and quantitative composition listing all components even if they do not end up in finished product
    - Include their functions
    - Amounts for each ingredient should be expressed per unit basis
    - Sub-formulations such as core, shell, colorants, coatings, flavors, inks etc should be described separately
    - Compendial requirements, for ex. EA numbers must be stated in EU submissions
    - Include composition as well as size, shape, color of capsule shells, if applicable.
    - Quality standards for all ingredients such as EP, USP, In-house etc. must be listed in the same table

DP Data-Components of Drug Product

- **Pharmaceutical Development (P.2)**
  - Components of the Drug Product (P.2.1)
  - For Generic dossiers a side by side comparison of RLD and proposed generic formulation is includes
  - A comparative testing of RLD with proposed drug is required by some agencies
  - Any deviations from RLD formulation should be addressed, discussed, and justified

DP Data-Formulation Development

- **Pharmaceutical Development (P.2)**
  - Drug Product (P.2.2)
    - Formulation Development
      - Summary of formulation with respect to dosage form and route of administration
      - Comparative dissolution is critical information for Generic oral solid dosages
      - Discuss the release mechanism if the proposed drug product is a modified release dosage ex. Emulsions
    - Overages
      - Overages must be identified in Table for P.1
    - Physico-chemical and biological properties
      - Discuss parameters impacting manufacturability and performance of the product
      - Many properties such as pH, osmolality, dissolution, dispersion, particle size fall in this category

DP Data-Manufacturing Process Development

- **Pharmaceutical Development (P.2)**
  - Manufacturing Process Development (P.2.3)
    - Justify the selection and optimization of the process described in P.3.3
    - Any differences that impacted the performance or manufacturability of the product should be indicated
    - Most recommended format is providing a table with batch number, batch use, batch size, manufacturing site , study number (if applicable) and specified equipment
    - Any significant equipment (design, operating principle, size, material) should be addressed

DP Data-Container Closure System

- **Pharmaceutical Development (P.2)**
  - Container Closure System (P.2.4)
    - Provide a brief description (details to be included in P.7)
    - Discuss suitability
      - Choice of material
      - Protection
      - Compatibility in terms of inertness (sorption as well as leaching)

DP Data-Microbiological Attributes

- **Pharmaceutical Development (P.2)**
  - Microbiological Attributes (P.2.5)
    - Address microbiological attributes of the drug product, drug substance, and excipients
    - Provide rationale for not performing microbial limits test on drug products (non sterile products only), drug substance and excipient
    - Container closure integrity test must be discussed for sterile injectable

DP Data-Compatibility

- **Pharmaceutical Development (P.2)**
  - Compatibility (P.2.6)
    - Compatibility of the drug product with diluents, if any
    - Compatibility of drug product with devices

DP Data-Manufactures

MANUFACTURE (P.3)

- **Manufacturers (P.3.1)**
  - Name, address and function of site(s) involved
  - Include manufacturers of drug product and also in-process materials (eg. Controlled release beads)
  - Packagers and labelers
  - Testing laboratories (testing finished products, intermediates, packaging components, stability etc.
  - Sites performing any sterilization operation
  - Establishment registration number (where applicable)

DP Data-Batch Formula

MANUFACTURE (P.3)

- **Batch Formula (P.3.2)**
  - List all components used in the process (processing agents such as water, nitrogen, silicone as well)
  - Provide their amounts including overages
  - Provide its quality standard
  - Separate batch formula is needed for separately formulated materials that are later combined

DP Data-Description of Manufacturing Process

MANUFACTURE (P.3)

- **Description of Manufacturing Process and Process Controls (P.3.3)**
  - Flow diagram showing steps of the process where materials enter the process
  - Show entire process from weighing of the components through release of the finished product
  - Show only critical process control
  - Indicate type of equipment used
  - Provide ranges only for critical operating parameter such as temperature, mixing time
  - Narrative should include everything mentioned above for the flow chart but in bit detail
  - Describe reworking or reprocessing if applicable

DP Data-Control of Critical Steps and Intermediates

- **MANUFACTURE (P.3)**
- **Controls of Critical Steps and Intermediates (P.3.4)**

  -All critical operating parameters (temperatures, time ranges, pH etc)

  -Environmental controls

  -In-process tests

  -list numeric ranges, limits, or acceptance criteria for each of the above control

DP Data-Process Validation

- **MANUFACTURE (P.3)**
- **Process Validation and/or Evaluation (P.3.5)**
  - In US this information must be submitted in cases of sterile product and only for those steps that are critical to sterility (eg. Sterilization)
  - Note: All finished product manufacturing processes should be validated since it is a cGMP requirement.
  - Some Agencies require a complete validation report
  - However, the validation information is reviewed during facility audits if Agency performs inspection

DP Data-Control of Excipients

- **Control of Excipient (P.4.1)**
  - Excipients are categorized as follows:
    - Compendial-non novel
      - Not much data is needed
    - Non-compendial—non novel
      - Some data is needed
    - Novel excipient (first time in human)
      - Data as much as drug substance needed
    - Excipient of human or animal origin
      - Critical information such as source and TSE/BSE free certificates is must

DP Data-Control of Excipients –(cont)

- **Control of Excipient (P.4)**
  - **Specification (P.4.1)**
    - Specification for all excipients must be provided
    - A citation to the appropriate official compendium
    - For non compendial, novel excipients specification and testing must reflect the safety
  - **Analytical Procedure (P.4.2)**
    - Detailed description of non compendial test procedures
    - Test methods for novel excipients are included in Appendix
  - **Validation of analytical procedures (P.4.3)**
    - All non compendial test procedures should validated
    - Include summary of method validation only

DP Data-Control of Excipients –(cont)

- **Control of Excipient (P.4)**
  - Justification of Specification (P.4.4)
    - Proposed excipient specification should be justified where appropriate
    - Justification may reference drug product stability data
    - For compendial excipients if additional testing is performed beyond the monograph then that testing and acceptance criteria must be justified

DP Data-Control of Excipients –(cont)

- **Control of Excipient (P.4)**
  - Excipient of Human or Animal Origin (P.4.5)
    - Identify
    - The genus, species, country of origin, source (eg liver) and manufacturer or supplier should be indicated
    - Provide BSE/TSE certificates

DP Data-Control of Excipients –(cont)

- **Control of Excipient (P.4)**
  - Novel Excipient (P.4.6)
    - Novel excipient are excipients used first time in human
    - Specification are included in this section
    - The level of other details included are same as drug substance and are provided in A.3

DP Data-Specification

- **Control of Drug Product (P.5)**
  - Specification (P.5.1)
    - Must establish Identity, Strength, Quality and Purity
    - Combination of analytical tests and acceptance criteria
    - Specification are acceptance criteria for the drug product that should be established per recommendation of ICH Q6A, applicable compendia, historical data
    - Combination of universal tests (identity, strength, quality and purity) specific tests that are critical for the performance and intended use the dosage form. For ex. Dissolution is critical to solid oral dosage, Bacterial endotoxins, sterility are necessary for sterile Injectables.
    - Provide a table of tests, test method reference and acceptance criteria
    - Indicate if acceptance criteria is applicable for release, shelf-life or both and indicate with an actual numerical value and/or range

DP Data-Analytical Procedures

- **Control of Drug Product (P.5)**
  - Analytical Procedures (P.5.2)
    - Market specific requirements are critical
    - For Ex. Japan requiring triplicate testing
    - Methods must be described if modified from a compendial method

DP Data-Validation of Analytical Procedures

- **Control of Drug Product (P.5)**
  - Validation of Analytical Procedures (P.5.3)
    - Analytical methods should be validated per ICH guideline Q2A and Q2B
    - Agency may require only validation summaries or compete validation reports

DP Data-Batch Analysis

- **Control of Drug Product (P.5)**
  - Batch Analysis (P.5.4)
    - A description of relevant batches and results of batch analyses should be provided
    - Batch description includes
      - Batch number and size
      - Batch number of the drug substance and novel excipient (if applicable) used
      - Container closure
      - Date and site of manufacture
      - Reference to the manufacturing process
      - Batch use (clinical, bioequivalence, primary stability etc)
    - Batch analysis reports (e.g., certificates of analysis (COAs) should be provided for all
    - Include data for the batches used for
      - (1) nonclinical studies (i.e., pharmacology and/or toxicology),
      - (2) drug product clinical efficacy and safety, bioavailability, bioequivalence
      - (3) primary stability studies

DP Data-Batch Analysis

- **Control of Drug Product (P.5)**
  - Batch Analysis (P.5.4)
    - Batch analysis report
      - Batch analysis report is expected where any changes to the manufacturing process and/or analytical methods should be discussed
      - Differences between older and new process or methods should be highlighted
    - Collated batch analysis data
      - Presentation of data for several batches in one table
      - Not warranted for every test but key tests such as assay, degradation product, moisture) can be represented this way

DP Data-Batch Analysis

- **Control of Drug Product (P.5)**
  - Characterization of Impurities (P.5.5.)
    - List all expected impurities (degradation products from DS and excipients, leachable from container closure)
    - Control of most of the impurities should be addressed in Drug Substance section except those not found in the DS should be discussed here

DP Data-Justification of Specification

- **Control of Drug Product (P.5)**
  - Justification of Specification (P.5.6)
    - Both tests and acceptance criteria should be justified
    - Justification for the proposed drug product specifications should be based on
      - Relevant historical development data (P.2.3)
      - Information on impurities (S.3.2)
      - Standards in an official compendium
      - Batch analyses data (P.5.4)
      - Stability studies (P.8)
      - Justify acceptance criteria for any in-process test that is performed in lieu of finished product test

DP Data-Reference Standard

- **Reference Standard (P.6)**
  - Reference Standard information for DS and its impurities is provided in section S.5
  - Include following information in case any impurity is unique to the drug product
    - Identify the source (official source such as USP or in house)
    - Provide characterization data if source is not official
    - Provide Certificate of Analysis

DP Data-Container Closure

- **Container Closure (P.7)**
  - Include following information for primary packaging
    - Table of all components (Type III DMF numbers and suppliers are required for US submissions, if applicable)
    - Material of construction
    - Relevant specification for ex. thickness blister foil
    - Some agencies require to include drawings, suppliers chemical tests and acceptance criteria
    - Some agencies require certificate of compliance
  - Justify choice of primary packaging by discussing
    - Compatibility (non reactive material)
    - Protection from moisture, light etc
    - Stability data provided in P.8.3 to further justify suitability of the container closure system

DP Data-Stability Summary and Conclusions

- **Stability (P.8)**
  - Adequate stability data is required of any submission and ideal is complete stability evaluation up to shelf-life
  - For global dossiers, data package varies from market to market in terms of stability evaluation conditions (Zones I-IV) and in terms of available data
  - Most agencies require minimum 12M of data on 3 batches per presentation under long term along with 6M of accelerated conditions (40 °C / 75% RH)
  - For multiple strengths, matrixing is acceptable by most Agencies
  - Data is expected in tabular format, reviewed and signed by QA
  - Provide conclusion regarding labeled storage conditions and shelf-life

ICH Climatic Zones for Stability Evaluations- products stored at Room Temperature

Climatic Zone	Long Term Testing Conditions for products stored at Room Temperature	Description
I	21 °C / 45% RH	Moderate
II	25 °C / 60% RH	Mediterranean
III	30 °C / 35% RH	Hot and Dry
IVa	30 °C / 65% RH	Hot and Humid
IVb	30 °C / 75% RH	Hot and Very Humid
Accelerated Testing condition is 40 °C / 75% RH		

Stability Evaluations conditions for products requiring special storage

Storage	Long Term Testing Conditions	Accelerated Testing Conditions
Refrigerated	5 °C ± 3 °C	25 °C ± 2 °C/60% RH ± 5% RH
Freezer	–20 °C ± 5 °C	5 °C ± 3 °C or 25 °C ± 2 °C or 30 °C ± 2 °C

Sampling and Testing Frequency

- Must be outlined in stability protocol
- Typical Testing Time points for finished product
- Not every parameter is evaluated at each time point
- Testing must cover complete shelf-life
- Long Term Evaluation
  - 0, 3, 6, 9, 12, 18, 24, 36 M
- Accelerated Conditions
  - 0, 3, 6 Months

DP Data-Stability Summary and Conclusions

- **Stability (P.8)**
  - Stability Summary and Conclusions (P.8.1) cont.
    - Analytical procedures are used to assure that the drug product meets acceptance criteria (specification) of identity, strength, quality and purity during its expiration dating.
    - It is implied that test methods used for stability batches are the ones included in P.5.2
    - In case of a different or alternative method is used it needs to described fully
    - Address the manufacturing differences and analytical procedure differences used for earlier stability batches

DP Data-Post Approval Stability Protocol and Commitment

- **Stability (P.8)**
  - Post Approval Stability Protocol and Commitment (P.8.2)
    - Summarize post approval study design if different than the one provided in (P.8.1)
    - Provide commitment regarding any ongoing or incomplete stability study

DP Data-Stability Data

- **Stability (P.8)**
  - Stability Data (P.8.3)
    - Include primary stability batches (pilot or commercial scale manufactured using process described in P.3.3)
    - Include supportive stability batches (smaller scale, earlier process, holding times for bulk tablets etc)
    - Stress studies
      - Include study design
      - Data is especially critical to the validation of analytical procedures
    - Present data in standard tabular format