الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Top Deficiencies in Phase II Validation

Version 1.0

Drug Sector

Saudi Food & Drug Authority

For comments regarding this document *Drug.Comments@sfda.gov.sa*

الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Drug Sector

Vision and Mission

Vision

To be the leading regional Drug Regulatory Authority for pharmaceuticals and cosmetic products, with professional excellence and services that contribute to the protection and advancement of public health in the Kingdom of Saudi Arabia.

الرؤية

أن يكون قطاع الدواء رائداً إقليمياً في الرقابة على الأدوية ومستحضرات التجميل، ويقدم خدماته بمهنية متميزة تسهم في حماية وتعزيز الصحة في المملكة العربية السعودية.

Mission

Protecting public health by ensuring safety, quality, efficacy and accessibility of human, veterinary drugs and biological products, and safety of cosmetics, through administration of a national regulatory system which is consistent with international best practice. Through our mission, we also provide accurate and scientific-based information to the public and healthcare professionals.

الرسالة

حماية الصحة العامة من خلال ضمان أمان وجودة وفعالية وتوفر الأدوية البشرية والبيطرية والمنتجات الحيوية وسلامة مواد التجميل عبر تطبيق نظام وطني للرقابة متوافق مع أفضل الممارسات الدولية وتقديم المعلومات الدوائية المبنية على أسس علمية للعامة والمهنيين الصحيين.

Document Control

Version	Author	Date	Comments
1.0	Drug Sector	3 September 2018	Final

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I. Drug Quality Data

a. Drug Substance(s)

1. The following information on DMF:
   - Name of the holder
   - DMF version number and date (yyyy-mm-dd) for the applicant's part and restricted part
   - If no changes were made within the last 5 years, a letter indicating that the DMF remains current

2. A valid Certificate of Suitability (CEP) (including any annexes) along with the required sections, where the CEP holder should duly fill out the Declaration of Access for the CEP

3. A written assurance that no significant changes to the manufacturing method have taken place following the granting of the certificate or its last revision

4. Clarification for the discrepancy in manufacturers between the application form (Section 1.2) (……) and the submitted 3.2.S (…….)

5. The following sections of the 3.2.S:
   - Control of materials (Section 3.2.S.2.3)
   - Control of critical steps and intermediates (Section 3.2.S.2.4)
   - Process validation and/or evaluation (Section 3.2.S.2.5)
   - Manufacturing process development (Section 3.2.S.2.6)

6. Detailed information on the starting material(s), including the following:
   - Name of the manufacturer(s)/supplier(s)
   - Route of synthesis
   - Specifications, which should be justified by supporting data
   - Scientific justification/rationale for selecting starting material(s)

7. Detailed information on description of manufacturing process and process controls (Section 3.2.S.2.2) as well as reagent(s) and residual solvents used in the route of synthesis, including specifications, which should be justified by supporting data

8. Detailed information on the elucidation of structure and other characteristics (Section 3.2.S.3.1) that includes studies to identify the potential polymorphic form(s)

9. Elucidation of structure and other characteristics (Section 3.2.S.3.1), including chromatograms

10. Sufficient evidence of acceptable risk/benefit proving that the genotoxic impurities do not form in the route of synthesis should be provided; screening of all chemical compounds that have been used in the route of synthesis using in silico software for potential genotoxicity might be done (refer to

Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk M7, Step 4 Version, 6. Hazard Assessment Elements)

11. Potential residues of class 1 solvents (e.g., benzene) in an intermediate or the final substance should be addressed because some originator solvents (e.g., acetone, toluene, ethanol, methanol, isopropanol, xylene, hexane, and petroleum ether) have been used in the route of synthesis (refer to CPMP/QWP/450/03 Rev. 1, Annex I, B: Class 1 Solvents Present as an Impurity)

12. Potential residues of class 1 solvents (e.g., carbon tetrachloride) in an intermediate or the final substance should be addressed because some originator solvents (e.g., chloroform and dichloromethane [methylene chloride]) have been used in the route of synthesis (refer to CPMP/QWP/450/03 Rev. 1, Annex I, B: Class 1 Solvents Present as an Impurity)

13. Batch analysis data from the API manufacturer and finished product manufacturer (Section 3.2.S.4.4)

14. Long-term stability studies up to the last available time points for the submitted batches

15. Detailed information on post approval stability protocol and stability commitments (Section 3.2.S.7.2), including a copy of the protocol

16. Clarification for the proposed retest period and storage conditions

b. Finished Product and Excipient(s)

1. Commitment to conduct ongoing stability studies (at least one batch per year)

2. Commitment to place the first three production batches on long-term stability studies through the proposed shelf life period

3. Commitment to conduct prospective process validation on three consecutive production batches (for nonsterile products)

4. Information on process validation for sterile products:
   - Media fill
   - Depyrogenation parameters
   - Validation of the sterile filter
   - Autoclave validation

5. Certificate of analysis for all primary packaging components

6. Minimum period covered for long-term stability studies at submission (12 months)

7. Production size range

8. In-use stability studies should be conducted in accordance with the GCC Guidelines for Stability Testing on at least two batches, taking into consideration the following requirements:

- Stability protocol to be submitted including: number of batch(s), size of batch(s), tested parameters, manufacturing date, and the starting date of the in-use stability study
- Study design simulates the use of the product in practice
- ONE of the batches should be chosen towards the END of its shelf-life (if available)

If such results are not available:

- ONE of the batches should be tested at the FINAL POINT of the submitted stability studies with
- A COMMITMENT to conduct in-use stability study at the END of shelf life and to report immediately any out of specifications to the SFDA

9. Compatibility studies of the drug product with the reconstitution diluents, taking into consideration the following requirements:
   - Studies preferably conducted on aged samples
   - Testing parameters in accordance with the specifications

10. Clarification for the discrepancy in the submitted information between the application form and the data submitted in the CTD

11. Release specifications (Section 3.2.P.5.1) that should have tighter limits than the shelf life specifications for stability-indicating parameters

c. Analytical Procedures and Validation

Drug Substance(s):

1. Full validation for the analytical procedures for assay, related substances, and residual solvents, including chromatograms

2. Partial validation/verification for the compendial analytical procedures for assay and related substances, including chromatograms

3. Chromatograms for specificity tests for the analytical procedures for residual solvents and related substances

4. Specificity and limit of detection (LOD) for benzene in the validation of analytical procedures for residual solvents

5. Certificate of analysis for the reference standard

6. Information on the calibration/validation of the working standard against the primary reference standard

7. Detailed information on the analytical procedure (Section 3.2.S.4.2), validation (Section 3.2.S.4.3), and reference standards (Section 3.2.S.5), including all chromatograms and acceptance criteria

8. Clear copies of chromatograms for specificity for the validation of analytical procedures

Finished Product:

1. Full information on the validation of all analytical procedures because only a summary was submitted

2. Full validation of the analytical procedures for assay, dissolution, and related substances including chromatograms

3. Partial validation/verification for the compendial analytical procedures for assay, dissolution, and related substances, including chromatograms

4. Verification for all analytical procedures from:
   - Release site(s)
   - Alternative site(s)
   - Sending and receiving laboratories (method transfer)

5. Validation for the analytical procedure(s) for the bacterial endotoxin test

6. Limit of quantitation (LOQ) for the verification of analytical procedure for related substances

7. Chromatograms for specificity for the validation of analytical procedures for assay and related substances

8. Certificate of analysis for reference standard (Section 3.2.P.6)

9. Information on the calibration/validation of the in-house standard against the primary reference standard

d. Bioequivalence

1. The bioequivalence study summary template

2. Comparative in vitro dissolution studies on PRODUCTION batches (including the calculation of similarity factor (f2)) according to the GCC Guidelines for Bioequivalence at different buffers (normally, pHs of 1.2, 4.5, and 6.8 and QC media) for the following:
   - Test vs. reference
   - Test vs. test (other strength)

Taking into consideration the following requirements:

- Submitting full details of the comparative study, including the type of apparatus, RPM, etc.
- Using 12 units of the product for each experiment to enable statistical evaluation
- The use of surfactant is not acceptable according to the GCC Guidelines for Bioequivalence

3. Chromatograms for at least 20% of the volunteers (consecutive number) along with chromatograms for calibration curves and QC samples, taking into consideration that each chromatogram should state the calculated concentration for each subject

4. Tabulated plasma concentrations (as a clear text, PDF, or Excel file) for each treatment (test and reference)

5. Expected production size range
6. The type and size of the biobatch
7. Solubility profile for the API (highest strength xx mg) in 250 mL or less of aqueous media over the pH range of 1.2–6.8 (for biowaiver applications)
8. Certificates of analysis for the test and reference products
9. Standard operating procedure (SOP) for the validation of bioanalytical method
10. Incurred sample reanalysis
11. Standard operating procedure (SOP) for sample reanalysis and reporting of final concentration
12. List of reanalyzed samples along with the reasons for reanalyzing them
13. Chromatograms of the original value and repeated value for the reanalyzed samples

II. Safety and Efficacy Data

1. Searchable and readable PDF documents in modules 2 and 5
2. Product information (SPC, PIL) with format consistent with GCC Guidance for Presenting SPC, PIL, and Labeling Information
3. SPC and PIL with related information content
4. Arabic PIL for all human drugs (including hospital only drugs) with consistent spelling and grammar and suitable public context
5. Generating product information content from suitable reference product (exact strength and dosage form)

III. Pharmacovigilance Data

1. Valid QPPV details and contact information
2. MAH statement to the effect that the applicant has the necessary means to fulfil tasks and responsibilities in the GVP
3. Reference to the location of the PSMF
4. Valid RMP under section 1.6.2

IV. Administrative Data

1. Clear and searchable PDF documents with no copy and paste restrictions

2. Consistent name, address, and role for finished product manufacturer stated in each of the following:

    - Application form
    - Artwork
    - CPP
    - Section 3.2.P.3.1