Drug File Validation Criteria

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This document is a draft published for comments and suggestions purposes. It is, therefore, subject to alteration and modification and may not be referred to as SFDA’s document until approved by SFDA.
Drug File Validation Criteria

Draft

Saudi Food & Drug Authority
Drug Sector

Please send your comments or suggestions before December 24, 2019 to:
Drug.comments@sfda.gov.sa

Saudi Food and Drug Authority

Vision and Mission

**Vision**

To be a leading international science-based regulator to protect and promote public health

**Mission**

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed
Document Control

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1. INTRODUCTION

1.1 Objective

This document initiated to control the practice of submitting the registration application that is not sufficiently complete. It highlights deficiencies to ensure completeness of the application and to avoid refusal the registration.

It is not meant to be a comprehensive list of deficiencies and requirement. Instead, it identifies certain requirements and certain recurrent deficiencies that in SFDA’s experience must led to a refusal.

SFDA evaluates each submitted application individually to determine whether the application is complete and sufficient to start the review process. Sufficiently complete means that the application contains all the information required to permit a substantive review.

1.2 Scope


1.3 Related Guidelines and Documents

This document should be read in conjunction with the following guidelines and documents published in the SFDA website (Drug Sector page):

- Registration Rules for Manufacturers and Pharmaceutical Products
- Regulatory Framework for Drug Approvals
- Guidance for Submission
- The GCC Data Requirements for Human Drugs Submission
- Top Deficiencies in Phase II Validation
2. VALIDATION PROCEDURE

Generally, after the online submission made via Saudi Drug Registration (SDR) system and the receipt of the dossier by the Drug Sector, the application will subject to several stages prior approval according to the following:

Deficiencies and requirements listed in this document applied to Business Validation, Evaluation and Inspection stages. During reviewing the submitted dossier for each stage, Drug Sector staff of the related departments will determine if there is any major deficiency that results in considering the application as incomplete to proceed the registration. Any identified major deficiency will results in a determination by SFDA that the application is incomplete and SFDA will therefore refuse to proceed the registration due to containing a major deficiency.
NOTE: For refused application, any resubmission in future will be considered as a new application.

3. MAJOR DEFFICIENCIES

SFDA expect to receive a dossier fulfill the requirements according to the GCC Data Requirements for Human Drugs submission and Guidance for Submission which represent a backbone for the submitted files. SFDA has the right to refuse the application that do not comply with these documents.

Each part in the following describes the major deficiencies and requirements for each registration stage that validation will based on.

3.1 Business Validation

- Application Form:
  - Drug Type:
    - The application type does not match the drug type.
  - Payment Method:
    - The applicant paid the wrong fees (e.g. paid the variation submission fee instead of new submission fee).
- Marketed in the country of origin (COO) for less than a year.
- The manufacturer has registered the same product previously in SFDA.
- For contract manufacturing products: the finished product manufacturer and marketing authorization holder (MAH) are not located in the same country.
- MAH does not have its own registered manufacturer in SFDA.
3.2 Evaluation Validation

3.2.1 Quality Evaluation

3.2.1.1 Active Pharmaceutical Ingredient (API)

- **Certificate of Suitability (CEP):**
  The dossier contains invalid CEP and/or the submitted supporting data for CEP was not according to the GCC Data Requirements for Human Drugs Submission (Please refer to “section 3.2.1 – 1 CEP”).

- **3.2.S/DMF:**
  
  i. The dossier contains incomplete or missing data including but not limited to the following deficiencies:
     o The restricted parts:
       - Detailed information on description of manufacturing process and process controls (Section 3.2.S.2.2).
       - Control of materials (Section 3.2.S.2.3).
       - Control of critical steps and intermediates (Section 3.2.S.2.4).
       - Manufacturing process development (Section 3.2.S.2.6).
     o Information on the starting material(s) (including the name of the manufacturer(s)/supplier(s), route of synthesis, specifications and certificate of analysis).
   
   ii. The sterility assurance data are missing for a sterile API.
   
   iii. Genotoxic impurities are presented in the route of synthesis and were not addressed in accordance with ICH M7 (R1).

   iv. Inadequate stability data was submitted including but not limited to the following deficiencies:
     o Number of batches.
     o Length of studies.
     (Please refer to “section 3.1 Active Pharmaceutical Ingredient (API)” of the GCC Guidelines for Stability Testing).

   v. Method (validation / verification / transfer) reports are not provided.
3.2.1.2 **Finished Pharmaceutical Products (FPP)**

- Inadequate stability data was submitted including but not limited to the following deficiencies:
  - Number of batches.
  - Length of studies.
  - Storage conditions.
  - Container Orientation.
  - Providing stability data on a different pack size, pack type, manufacturing site that intended to be marketed in KSA.
  - Not providing stability data on batches manufactured by using the proposed API source(s).
  - The compatibility studies according to the GCC Guidelines for Stability Testing were not submitted.
  - The in-use stability studies according to the GCC Guidelines for Stability Testing were not submitted.
    (Please refer to “section 3.2 Finished Pharmaceutical Product (FPP)” of the GCC Guidelines for Stability Testing).

- **Formulation:**
  - Overage in the drug substance used to compensate the degradation or to extend shelf life.
  - Inactive ingredients are exceeding the FDA inactive ingredient database limit without sufficient justification to support the safety of the inactive ingredients at the proposed level.

- **Microbiology considerations:**
  An application should contain all sterility assurance validation studies for terminally sterilized drug products and aseptically filled drug products, as described below:
  - Terminally sterilized drug products:
    - Validation of production terminal sterilization process.
− Validation of depyrogenation of product containers and closures.
− Validation of container-closure package integrity.
  o Aseptically filled drug products:
    − Validation of the sterilizing grade filters (bacterial retention studies).
    − Validation of the sterilization of sterile bulk drug or product contact equipment, components, containers and closures.
    − Validation of the depyrogenation of product containers and closures.
    − Validation of the aseptic filling process (media fills/process simulations).
    − Validation of container-closure package integrity.
  • Method (validation/verification/transfer) reports are not provided.
  • For Biological products:
    o (3.2.R) Biosimilar:
      Missing or incomplete a comparability studies for biosimilar (3.2.R).

3.2.2 Benefit and Risk

3.2.2.1 Bioequivalence (BE)

  • The bioequivalence study is conducted in a suspended Contract Research Organization (CRO).
  • Using a suspended API source in the biobatch.
  • The biobatch size is not in accordance with GCC Guidelines for Bioequivalence.
  • The parametric 90% Confidence Interval (C.I.) of Cmax or AUC0-t for test/reference ratio are out of acceptance limits.
  • The study design (under fasting and/or fed conditions) is not in accordance with GCC Guidelines for Bioequivalence.
  • The selection of reference product is not in accordance with GCC Guidelines for Bioequivalence.
  • For modified release formulation:
    o The biobatch is not manufactured at the proposed manufacturing site.
    o The dossier does not contain a required studies (bioequivalence studies under fasting and fed conditions).
• Biowaiver (based on Biopharmaceutics Classification system “BCS”) study report for BCS class II, III and IV drugs.

3.2.2.2 Clinical evaluation

• Does not have essential clinical modules including: Module 2.5 structured according to ICH Efficacy – M4E.
• Lacks tabular listing of clinical studies.

3.2.2.3 Summary of Products Characteristics (SPC) and Patient Information Leaflet (PIL)

• Missing or not relevant product information (Module 1.3.1, 1.3.3):
  Either SPC, ePIL or aPIL is missing from the dossier or not relevant to the submission.
• Layout of submitted product information is not in accordance to GCC Guidance for presenting SPC, PIL, and labeling information:
  The layout of the submitted SPC or PIL is not in accordance to GCC Guidance for Presenting the SPC, PIL and labeling information.

3.3 Inspection

• Suspended by SFDA or GCC until the suspension revoked.
• Rejected by SFDA or GCC until one year pass from the date of rejection decision.
  The company need to submit corrective actions prior any further steps.

3.4 Appeal Process

The applicant has the right to appeal against the decision within 60 calendar days