الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Regulatory Guidance for Literature Based Support of Efficacy and Safety of Medicines

Version 1.0

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Saudi Food & Drug Authority

Drug Sector

For Comments *Drug.Comments@sfda.gov.sa*

Please visit SFDA's website for the latest update

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

Version	Author	Date	Comments
Draft	Benefit and Risk Evaluation Executive Directorate	18 December 2024	-
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List of abbreviations

API	Active Pharmaceutical Ingredient
eCTD	electronic Common Technical Document
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCC	Gulf Cooperation Council
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
KAS	Known active substance
LBS	Literature-based submission
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare products Regulatory Agency
NCE	New Chemical Entity
PMDA	Pharmaceuticals and Medical Devices Agency
SFDA	Saudi Food & Drug Authority
SRA	Stringent Regulatory Authority
Swissmedic	Swiss Agency for Therapeutic Products
TGA	Therapeutic Goods Administration

Definitions

Active Pharmaceutical Ingredient (API)	A substance in a drug that is responsible for its therapeutic effect.
Applicant	Drug applicant refers to an individual, organization, or entity that submits the drug application to SFDA for approval to market a new drug or a drug with a new indication.
Common Technical Document (CTD)	An international harmonized format for submissions for approval of pharmaceuticals. The CTD provides a standardization of the presentation of the content.
Generic product	A product created to be equivalent to the innovative / brand name product in dosage form, strength, route of administration, quality, performance characteristics and therapeutic indication(s). A drug application will be considered as generic if the innovative product is registered in one of the SRA irrespective of whether the innovative product is registered or not at SFDA.
Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)	A systematic approach is used to assess the quality of evidence and strength of recommendations in clinical practice guidelines and systematic reviews. It ensures that recommendations are based on the best available evidence and presented in a transparent and consistent manner.
Inquiry	A questions or clarifications submitted through the SDR system to be answered by the applicant.
Known active substance	A new dosage form, strength, route of administration or indication of an active ingredient already marketed in Saudi Arabia.
Literature review or literature-based submission	It is a scholarly assessment of existing research and publications on a specific topic or research question. It involves systematically gathering, evaluating, and synthesizing relevant studies, theories, and findings to offer a comprehensive overview of the current understanding in the field.

Medical Subject Headings (MeSH)	It is a controlled vocabulary system used by the National Library of Medicine (NLM) to index and catalog biomedical and health-related information. index and catalog biomedical and health-related information. It is designed to facilitate the effective searching and retrieval of relevant information from databases such as PubMed.
Marketing Authorization Applications (MAAs)	A formal submission made by pharmaceutical companies to regulatory authorities seeking approval to market a new medicinal product.
New chemical entity (NCE)	A product that includes new chemical entity and introduced by the innovator company (or the partner).
Reference product	An approved drug product that serves as the standard for comparison when assessing new drug products. It provides a benchmark to ensure that new drugs, such as generics, are equivalent in terms of safety, efficacy, and quality.
Stringent Regulatory Authority (SRA)	A regulatory body that enforces stringent requirements for the approval and monitoring of medical products and practices USFDA, EMA, MHRA (UK), Swissmedic, Health Canada, TGA (Australia), and PMDA (Japan).

1. INTRODUCTION

The evaluation process for marketing authorization applications (MAAs) relies on the quality of the submitted clinical data. Upon receiving the MAA, the SFDA conducts an initial validation to ensure the completeness of the application and its adherence to regulatory requirements. The application then undergoes a thorough review by regulatory reviewers, who analyze the scientific data and documentation to assess the product's safety, efficacy, and quality. To obtain marketing authorization for new medicines, it is required to demonstrate a favorable benefit-risk profile through clinical studies, as outlined by SFDA related documents. Typically, these studies are sponsored by the applicant. However, in cases where applicant-sponsored trials are unavailable, the SFDA may accept literature references to these trials. This applies to:

- New generic applications when the reference product is not registered by the SFDA.
- New drug applications for known active substance (KAS).

If the submission is incomplete or requires further clarification, the applicant is expected to thoroughly analyze any literature-based inquiries that arise and address all aspects clearly, concisely, accurately, and ensuring that the required data is incorporated into the appropriate eCTD application. Meeting regulatory requirements helps avoid unnecessary delays and facilitates better regulatory decisions.

1.1. Purpose

This guidance aims to standardize and improve the quality of clinical data for literature review-based submissions.

1.2. Scope

This guidance assists applicant on the required clinical data for generic (multisource) products and known active substance, when the reference innovator is not registered by the SFDA. It also encompasses the need for applicants to provide justification for any technical claims made in their clinical development program.

1.3. Related documents

This document should be read in conjunction with the following Drug Sector documents:

- *Data Requirements for Human Drugs Submission*
- *Clinical Considerations for Efficacy and Safety*
- *Regulatory Framework for Drugs Approval*
- *Guidelines for Bioequivalence*

2. APPLICATION SUBMISSION

2.1. Pre-submission meeting[1]

The applicant is advised to request a meeting three months prior to submission to discuss the literature-based submission in term of:

- Rational behind submitting this application:
  - Objective of the submission; new drug approval, new indication … etc
  - Outline the anticipated benefits; improvements in patient outcomes, advancements in treatment, address unmet medical needs
- Type of medicinal product (new, generic, known active substance)
- Clinical data requirements
- Literature search methodology

2.2. Clinical data requirements

The data must be submitted in accordance with the eCTD structure. The clinical data requirements for each application varies based on the product type:

2.2.1. Generic products (whether active pharmaceutical ingredient (API) is registered or not, the applicant must refer to **SFDA bioequivalence guideline**).

- For new generic product of an SFDA registered reference product: refer to the SFDA bioequivalence guideline on the SFDA website.

[1] To schedule a formal meeting with the Drug Sector, please adhere to the outlined 'Requirements for Formal Meeting between Drug Sector and Applicants'

- For new generic product of a non-SFDA registered reference product: The required data for literature-based submissions (LBS) varies depending on the worldwide registration status of the reference and/or generic products, as detailed in **Table 1**:

Table 1	
Generic products are registered in SRA	**Generic products are not registered in SRA**
In the context of the electronic Common Technical Document (eCTD) format, to establish efficacy and safety, the applicant should provide the relevant information in Module 1 and 2, specifically the following: **Module 1:** ➢ 1.4: Information on the expert ▪ 1.4.3: Clinical **Module 2:** ➢ 2.5: Clinical Overview ▪ 2.5.1: Product Development Rationale ▪ 2.5.2: Overview of Biopharmaceutics ▪ 2.5.3: Overview of Clinical Pharmacology ▪ 2.5.4 and 2.5.5: Overview of Efficacy and Safety: provide the following information: o Literature based submission contains a literature review to support efficacy and safety of the active ingredient in each proposed indication. If the evidence is not substantial, conduct a meta-analysis of clinical data. (Note: Orphan drugs may be exempted). o The search methodology should be stated (e.g. use of key words, databases, filters, and date and time when the search was	In the context of the electronic Common Technical Document (eCTD) format, to establish efficacy and safety, the applicant should provide the relevant information in Module 1 and 2, specifically the following: **Module 1:** ➢ 1.4: Information on the expert ▪ 1.4.3: Clinical **Module 2:** ➢ 2.5: Clinical Overview ▪ 2.5.1: Product Development Rationale o Address the current marketing registration status. ▪ 2.5.2: Overview of Biopharmaceutics ▪ 2.5.3: Overview of Clinical Pharmacology ▪ 2.5.4 and 2.5.5: Overview of Efficacy and Safety: provide the following information: o Literature based submission contains a **systematic** literature review to support efficacy and safety of the active ingredient in each proposed indication. If the evidence is not substantial, conduct a meta-analysis of clinical data. (Note: Orphan drugs may be

conducted) ○ Tabular listing of the identified literatures (see Section 3.5.C.). ○ Serious adverse events related to the product (from randomized controlled trials and observational studies) as well as periodic safety update reports (PSUR) of the reference product. ▪ 2.5.6: Benefits and Risks Conclusions ▪ 2.5.7: References ○ Ensure literature references are included as full texts in separated PDF files	exempted). ○ The search methodology should be stated (e.g. use of key words, databases, filters, and date and time when the search was conducted) ○ Tabular listing of the identified literatures (see Section 3.5.C.). ○ Serious adverse events related to the product (from randomized controlled trials and observational studies) as well as post marketing safety studies. ▪ 2.5.6: Benefits and Risks Conclusions ▪ 2.5.7: References ○ Ensure literature references are included as full texts in separated PDF files

2.2.2. Known active substance product (known as active pharmaceutical ingredients) is a drug product containing active pharmaceutical product that is already marketed in Saudi Arabia in a different dosage form, strength or therapeutic indication, the data requirements for these products may vary based on several factors. Therefore, the SFDA will assess each case individually and determine whether literature-based submission is sufficient to confirm the medicinal product's efficacy and safety or if additional clinical data (e.g. company sponsored trials) are necessary.

The applicants must fill the table in **Appendix 1**, which should include a summary report of the Clinical Overview that encompasses:

- Clinical development program (if any)
- Literature search methodology
- Tabular listing of recent studies
- Efficacy and safety study results
- List of relevant literature references.

3. LITERATURE SEARCH STRATEGY

A literature search strategy involves a structured approach to finding relevant research and information on a specific topic.

The key components of a literature search strategy are:

3.1. Formulate the question

- Using PICO which is a specialized framework to formulate a research question and to facilitate literature review. It consists of four components:
  - ✓ **P:** Patients, Populations or Problems. What are the characteristics of patient or population?
  - ✓ **I:** Intervention. Is it therapeutic, diagnostic, or experimental intervention?
  - ✓ **C:** Comparison. What is the alternative to intervention?
  - ✓ **O:** Outcome. What are the relevant outcomes?

3.2. Search the literature

- Identify relevant database using PubMed (a free online search engine which support the search and retrieval of literature from MEDLINE)
- Subject searching/MeSH terms using ANDOR (also known as *Boolean operators*). Use limits/filters provided
- Keep a record of the keywords and methods used in searching (for describing how the search was conducted)

3.3. Screen for inclusion

- Review abstracts to decide their relevance to the research question then obtain the full-text article for quality assessment.

3.4. Assess quality of evidence

- Using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) Working Group which is a set of evidence-based criteria to grade the quality of evidence. GRADE considers study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias. For more details, see **Appendix 2**.

3.5. Extract, analyze and report data

- The Cochrane Handbook for Systematic Reviews of Interventions is a comprehensive guide designed to assist in the process of conducting systematic reviews, including data extraction, analysis, and reporting.

A. Data extraction: it involves systematically gathering relevant information from included studies to ensure accurate and consistent data collection.

- Steps for data extraction:
  - ✓ Create a standardized form to collect necessary data from each study.
  - ✓ Document information such as the study design, participant demographics, details of the intervention and comparator, and outcome measures.
  - ✓ Extract data on primary and secondary outcomes, including effect sizes, confidence intervals, and any measures of variability or heterogeneity.
  - ✓ Identify any reported biases in the studies and gather pertinent information on bias assessments.
  - ✓ Ensure that at least two reviewers independently extract the data to reduce errors, and address any discrepancies through discussion.

B. Data analysis: it involves synthesizing and interpreting the extracted data to provide evidence that supports decision-making.

- Steps for data analysis:
  - ✓ Assess risk of bias by apply tools such as the Cochrane Risk of Bias Tool 2 for randomized controlled trials and the Robinson tool for non-randomized controlled trials.
  - ✓ Conduct meta-analysis if appropriate, using statistical methods to combine data from multiple studies. If not applicable (due to reasons such as a limited number of studies reporting the same

outcome, low study quality, etc.), then the data may be systematically summarized.

C. Reporting data: it involves presenting the findings of the systematic review in a clear and structured manner to enhance comprehension and practical application.

- Steps for reporting:
  - ✓ Structure the literature review to include introduction, methods, results, discussion, and conclusion.
  - ✓ Arrange the identified literature with their citations in a tabular listing as follows:
    - Start with the key clinical studies (e.g. confirmatory studies).
    - Prioritize well-designed studies that are adequately powered and, ideally, multicenter. If a meta-analysis was performed, please complete the table in **Appendix 3**.
    - Include studies with registered protocols or those listed in clinical trials registries (indicate their registration status)
    - Place evidence from non-randomized controlled trials in a separate section of the table.
    - Clinical study reports for each identified study, if possible.

Appendix 1:

<table>
<tr><th colspan="2">Product information and data submission</th></tr>
<tr><td>Reference #</td><td></td></tr>
<tr><td>Product name</td><td></td></tr>
<tr><td>Active ingredient</td><td></td></tr>
<tr><td>Dosage form/strength</td><td></td></tr>
<tr><td>MAH</td><td></td></tr>
<tr><td>Type of medicinal product</td><td>o Generic
o Known active substance</td></tr>
<tr><td>Information on the expert</td><td>Name of the expert
Affiliation
Qualification
Signature
Date of signature</td></tr>
<tr><td>Approval and marketing status of the product</td><td><table><tr><th>Approval status:</th></tr><tr><td>o SRA: state the country
o Non-SRA: state the country
o No</td></tr><tr><th>Marketing status</th></tr><tr><td>o Marketed
o Not marketed</td></tr></table></td></tr>
<tr><td>Indication/s</td><td></td></tr>
<tr><td>Clinical development program by the company</td><td>o No:
o Yes: refer to the trials sponsored by the MAH</td></tr>
</table>

Methodology	○ *Database:* ○ *Keywords:* ○ *Filter applied:* ○ *Date and time of the search:* ○ *Number of studies:* ○ *Data extraction:* ○ *Data analysis:*
Tabular listing of identified literature for each proposed indication (start with key studies)	○ *Citation:* ○ *Registration status (if any):* ○ *Study design:* ○ *Objective/s:* ○ *Treatment arm/s:* (dose, frequency, route and duration) / (number of patients [entered/completed]) ○ *Study population:* ○ *Primary endpoint/s:* ○ *Study findings (efficacy):* focus on primary objective/s ○ *Study findings (safety):* focus on series/common side effects

Appendix 2:

<table>
<tr><th colspan="4">GRADE's approach to rate quality of evidence</th></tr>
<tr><th rowspan="2">Study design</th><th colspan="3">Quality of evidence</th></tr>
<tr><th>Grade</th><th>Lower if</th><th>Higher if</th></tr>
<tr><td rowspan="2">Randomized trial</td><td>High</td><td rowspan="3">• Risk of bias
-1 serious
-2 very serious

• Inconsistency
-1 serious
-2 very serious

• Indirectness
-1 serious
-2 very serious

• Imprecision
-1 serious
-2 very serious

• Publication bias
-1 Likely
-2 Very likely</td><td rowspan="3">• Large effect
+1 Large
+1 Very large

• Dose response
+1 Evidence of a gradient

• All plausible confounding
+1 Would reduce a demonstrated effect, or
+1 Would suggest a spurious effect when results show no effect</td></tr>
<tr><td>Moderate</td></tr>
<tr><td rowspan="2">Observational study</td><td>Low</td></tr>
<tr><td>Very low</td><td></td></tr>
</table>

Appendix 3:

To be completed in case of meta-analysis provided by the applicant:

Title: <title> {as indicated on the study report}		
Reference	-Use sponsor protocol number or clinical trials registry identifier-	
Rationale		
Objectives		
Methods	-PRISMA guidelines/ Study selection and the systematic review definition of objectives with clinical relevance follow the Population, Intervention, Comparison, Outcome, and Study Type (PICOS) method-	
Inclusion and Exclusion criteria	-Summary of the main criteria; however,for details on inclusion and exclusion criteria refer to the Appendix-	
Data integrity	**Registration status in clinical trials registries**	
	Protocol amendments	{listed and how many times have it occured, detailed in the Appendix}
	Protocol deviations	{check for issues related to protocol deviation and protocol change and how that could affect the outcomes}
	Randomization and blinding	{check randomization and blinding types implemented in the study} -Methods used to generate the random allocation sequence and stratification criteria to implement it-
	Other aspects	{If available}
Statistical analysis	-Were all the included studies analyzed-	
Heterogeneity		
Information sources		
Search strategy		
Data analysis	-Data synthesis, assessment of the quality of the data and missing data-	
Treatment arms *-Add as many rows as needed to describe the*	Arm 1<treatment>. <duration>, <number randomized>	
	Arm 2<treatment>. <duration>, <number randomized>	

treatment groups-		
Endpoints and definitions *-Add as many rows as needed to describe the endpoints; for the secondary endpoints select the ones considered most relevant and reported in the results section-*	**Primary endpoint(s)**	{provide brief description}
	Secondary endpoint(s) **<other: specify (Exploratory)> endpoint**	{provide brief description}

4. REFERENCES

1. ICH E3 Structure and content of clinical study reports
2. ICH guideline M4 (R4) on common technical document (CTD) for the registration of pharmaceuticals for human use
3. Pre-submission guidance for literature-based submissions (LBS) | Therapeutic Goods Administration (TGA)
4. Dossier requirements for literature based submissions | Therapeutic Goods Administration (TGA)
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6. Guidance Document: Drug Submissions Relying on Third-Party Data (Literature and Market Experience). Health Canada
7. Guidance Document: Authorization of human medicinal product with known active substance \ SwissMedic
8. Guidance on Conducting a Systematic Literature Review - Yu Xiao, Maria Watson, 2019 (sagepub.com)
9. GRADE handbook (gradepro.org)
10. Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training
11. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials | Cochrane Bias
12. ROBINS-I | Cochrane Bias