الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Clinical Considerations for Efficacy and Safety Assessment

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Drug Sector

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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

Pharmaceutical and biological products submitted for SFDA's assessment and authorization must meet many aspects of quality, safety and efficacy. The overall evaluation process depends on the quality of submitted relevant clinical data. Assessment of the benefit-risk balance of products depends on evaluating the clinical components of the application. All pharmaceutical and biological products intended for human use must undergo certain clinical testing via a series of studies to establish their safety and efficacy profile. The number and type of studies needed depends on the type of application. This document describes the clinical data required for drug registration at the Saudi Food and Drug Authority (SFDA).

2. SCOPE

This guidance provides recommendations on the clinical data requirements for Human medicinal and biological products. It applies to data supporting new applications for drug, biologic, generic drug applications and type II variations regarding changes to therapeutic indications. The Information discussed in this document does not apply to veterinary and herbal product submissions. This document is meant to be a guidance tool for applicants to ensure the availability of minimum clinical data required in the submission to establish the safety and efficacy of the product. The SFDA encourages applicants to discuss the outcome of the clinical evaluation, if needed, in the context of this guidance.

3. RELEVANT DOCUMENTS

This guidance should be read in conjunction with:

- Data requirements for human drugs submission
- Regulatory framework for drugs approval
- Guideline for bioequivalence
- Clinical considerations for vaccines
- Guidelines on Biosimilar Products: Quality Considerations
- The GCC Guidance for presenting the labeling information, Summary of product characteristic (SPC) and Patient information leaflet (PIL).
- Guidelines for variation requirements

International Council for Harmonization (ICH) guidelines:

- ICH E1: Clinical Safety for Drugs used in Long-Term Treatment
- ICH E3: Clinical Study Reports
- ICH E4: Dose-Response Studies
- ICH E5: Ethnic Factors
- ICH E6: Good Clinical Practice
- ICH E7: Clinical Trials in Geriatric Population
- ICH E8: General Considerations for Clinical Trials
- ICH E9: Statistical Principles for Clinical Trials
- ICH E10: Choice of Control Group in Clinical Trials
- ICH E11: Clinical Trials in Pediatric Population
- ICH E12: Clinical Evaluation by Therapeutic Category
- ICH E17: Multi-Regional Clinical Trials
- ICH E19: Safety Data Collection

For biological products containing blood products and biosimilars medicines, please refer to European Medicinal Agency (EMA) guidelines on blood products including biotech alternatives (https://www.ema.europa.eu).

4. DEFINITIONS

- **New chemical entity:**

  A drug molecule that has never been marketed in Saudi Arabia.

- **Known active substance:**

  A new dosage form, strength, route of administration or indication of an active ingredient already marketed in Saudi Arabia.

- **Biological drug:**

  Medicinal products derived from a variety of natural sources or produced by biotechnology methods and other cutting-edge technologies. They include a wide range of products such as vaccines, blood and blood components, allergenics, advanced therapy medicinal products (ATMPs), recombinant proteins and biosimilars.

- **Biosimilar drug:**

  Therapeutic proteins produced by recombinant deoxyribonucleic acid (DNA) technology or gene expression method following the footsteps of one licensed reference biotechnological product. They are complex and heterogeneous in their nature; hence they are not considered generics, but as closely similar to the innovator's drug as possible.

- **Blood product:**

  They are a wide range of medicinal product sourced from human blood or plasma (source material) that can be collected and tested at "Blood Establishments" and obtained by industrial process "Fractionation" of human plasma of a large number of donations (up to tens of thousands) that are pooled together.

- **Vaccine:**

  Preparations that contain antigenic substances capable of inducing a specific and active immunity against the infecting agent or the toxin or the antigen produced by it.

- **Generic drug:**

  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). SFDA considers drug applications as generic if the innovative is registered in one of the SRA irrespective of whether the innovative product is registered or not at SFDA.

- **Fixed combination product**:

  Combination of two or more active substances in a fixed ratio of doses within a single dosage form as a final drug product. The two or more active ingredients are used concomitantly as separate single active substances products for a combination therapy regimen and/or used separately for different indications.

5. CLINICAL DATA REQUIREMENTS ACCORDING TO TYPE OF SUBMISSION

Every submission to the SFDA must include a minimum supporting clinical data to ensure that the product is safe and efficacious/effective to be used in humans. All evidence submitted must comply with good clinical practice (GCP) guidelines. Further, data integrity is the responsibility of the applicant. The SFDA encourages the use of local data as part of clinical development programs yet foreign data can be accepted. To ensure data integrity and GCP compliance, the SFDA may assess and inspect any site used in the clinical development program.

5.1. New Marketing Authorization Application

5.1.1. New chemical entity

For new chemical entities, a full clinical development program is required. The clinical development program should aim to establish the clinical efficacy and safety of the product when administered to the target recipient using the proposed dosage form through the intended route of administration. Knowledge established should include appropriate dose regimen, pharmacokinetic and pharmacodynamic parameters, target population and safety and efficacy estimates. The clinical development program should generally include the following:

1. *Phase I clinical trial(s):*

   The objective of these trials should be providing safety (tolerability) and pharmacokinetic (PK) data for the new drug. Usually conducted in healthy volunteers and include (first in human trial).

2. *Phase II clinical trial(s):*

   In these trials of the development program, the aim should be establishing proof of mechanism, identifying the targeted patient population and/or determining the optimal dose regimen (dose escalation trials). Evaluating pharmacokinetics and pharmacodynamics (PD) and therapeutic exploratory data could be included in these trials.

3. *Phase III clinical trial(s):*

   These trials are confirmatory large-scale trials structured to provide extensive information regarding the safety and efficacy of the product. All information generated

in previous trials should be used to design the most appropriate outcome measures in order to provide sufficient safety and efficacy data.

The clinical development program must clearly indicate the body of evidence supporting the safety and efficacy. A tabular listing of all included trials should serve to indicate the studies deemed pivotal and the ones considered supportive evidence. The program must sufficiently show in what patient population was efficacy demonstrated and why was this population chosen to be studied. If the proposed indication covers a broader population than what was in the clinical development program, scientific rational and justification should be explicitly discussed. The proposed duration of treatment for each indication must be supported by clear data from the program. All trial documents must be submitted in the application along with the clinical study report (CSR) for every trial including individual patient data. Clinical study reports must be provided in ICH E3 format.

All trials must be conducted according to the provided study protocol which should be registered in a clinical trial registry that is accessible by SFDA. All amendments and deviations from protocol must be provided. The clinical trial protocol is expected to cover, but not limited to the following:

- Objectives and hypothesis, trial design, randomization and blinding, primary and secondary endpoints and their measurements, exploratory endpoints and their rational, study population and key inclusion and exclusion criteria, rational for the choice of control, statistical analysis and sample size calculation.
- Studies using a master protocol approach, platform design, seamless trial designs and combined phases are acceptable as part of the clinical development program. However, the applicant should state clearly if the submission includes the whole study or only the part relevant to the marketing authorization application.
- Observational studies intended to test effectiveness and safety, or what is often called Real World Evidence, do not substitute randomized controlled trials. However, if used, they may support the conclusion of a clinical development program based on clinical trials.
- In case of any omitted parts of the clinical development program, justifications should be explicitly discussed in the submission. Examples of cases where an incomplete development program could be accepted include drugs for rare diseases and breakthrough medications. In such cases where approval is granted on the basis of an incomplete development program and/or interim results, it is

the responsibility of the applicant to submit the completed results of the trials to the SFDA as soon as they become available.

5.1.2. Known active substance:

(i) Known active substance with a new pharmaceutical dosage form, strength, or route of administration:

Applications of new products using a new pharmaceutical dosage form, route of administration or strength of an active substance already registered needs to include evidence composed of clinical data supporting the safety and efficacy of the proposed product. Data should include safety and tolerability studies showing that the new dosage form/route/strength is not in any way more harmful to the patients than the approved one. In addition, the applicant must establish the efficacy of the new product by either a clinical trial with a clinically relevant endpoint to the intended indication or a trial showing comparable pharmacokinetic/pharmacodynamics parameters to the approved product. Data from the approved dosage form/route/strength can be used as supportive evidence for the new product if the applicant submitted acceptable evidence that these data are applicable to the new product.

(ii) Known active substance with a new indication or dosage recommendation that has not been previously authorized:

Applications of new products containing an active substance already approved and the new product is intended for a different indication, or a different dosage recommendation need to include clinical data supporting the safety and efficacy of the proposed indication or dosage recommendation. Clinical data is expected to include a phase two/three trial(s) designed to establish the desired dose and demonstrate the efficacy and safety of the new proposed indication or dosage recommendation.

(iii)Fixed combination product:

- Application of products containing a fixed-dose combination of two or more known active substances with the same dosage form, strength and indications that already approved and intended for use as a substitution therapy in patients already using the two (or more)

substances concomitantly as separate products should include rationale of the development of this combination product. The rationale should justify combining the two substances in terms of improving adherence, reducing medication errors or other relevant advantages proposed by the applicant. Combining active ingredients should be supported by evidence showing safety of the concomitant use of the two ingredients. In addition, the applicant must provide evidence of bioequivalence of the new combination product to the registered reference products (see GCC guidelines for bioequivalence).

- If the applicant seeks a new therapeutic indication for the combination product, clinical evidence to support the indication, most likely a phase two/three clinical trial is needed.

5.1.3. Biological

For new biological products, the applicant must provide a full clinical development program. (Please refer to section 5.1).

5.1.4. Biosimilar

Biosimilar products are biologics that are supposed to be highly similar to an approved biologic reference product. Due to the biologic nature of these products and the differences arising from different biologic sources, case by case approach is being followed in determining what is essential to demonstrate biosimilarity to the reference.

The following considerations should be taken into account when submitting a biosimilarity development program:

1. Dosage form, strength, and route of administration of the biosimilar should be identical to the reference product. If not, the applicant must provide justifications.
2. The same reference product should be used throughout the comparability development program and any changes made should be justified.
3. The source of the reference biologic used in the comparability studies should be the same as the one registered at SFDA. If a different source is used, the applicant must provide evidence that supports bridging data between the two reference products.
4. If the reference biologic product is not SFDA registered, the applicant should provide clinical data that support the safety and efficacy of each submitted therapeutic indication. Such data would be the whole clinical development program of the reference or

accumulated published clinical trials including the pivotal trials of the reference. In such cases, the applicant may be exempted from submitting clinical trials according to the ICH E3 guideline. However, tabulation and structure must be in line with clinical requirements highlighted in section 5.3.2 New generic drug of a non-SFDA registered reference product.

5. The comparability exercise between the biosimilar and the reference biologic product must meet the quality standards such as outlined in the ICH Q5E guideline and SFDA's Guidelines on Biosimilar Products: Quality Considerations.
6. The applicant should provide well conducted clinical trial(s) assessing the immunogenicity, pharmacokinetic and/or pharmacodynamic parameters of the new proposed biosimilar to the reference product.
7. Clinical comparability needs to be established using a well conducted clinical trial. The choice of the indication, endpoints and population used in the study should be justified and discussed in details as usually the most sensitive population and indication should be used. The trial should be designed to provide comparable safety and efficacy clinical data to the reference.
8. All sites used for the development program must be approved by SFDA
9. Extrapolating approval of biosimilar to other indications approved for the reference product not studied in the clinical comparability study is possible. The applicant should discuss in details the scientific justification for each proposed indication extrapolation. Clinical experience with the reference product, the mechanism of action, and the target receptors involved play a role in determining which extrapolation will be accepted. However, only SFDA approved indications for the reference biologic product will be considered.
10. The SFDA adopts the European Medicines Agency guidelines for the following biosimilar medicines:

Type of biosimilar medicine	Adopted guidelines
Biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor	EU Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, EMEA/CHMP/BMWP/42832/2005 Rev. 1
Biosimilar medicines containing low-molecular-weight heparins	EU Non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins, EMEA/CHMP/BMWP/118264/2007 Rev. 1
Biosimilar medicines containing recombinant human insulin and insulin analogues	EU Non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues, EMEA/CHMP/BMWP/32775/2005 Rev. 1
Biosimilar medicines containing interferon beta	EU Similar biological medicinal products containing interferon beta, EMA/CHMP/BMWP/652000/2010
Biosimilar medicines containing monoclonal antibodies	EU Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues, EMA/CHMP/BMWP/403543/2010
Biosimilar medicines containing recombinant erythropoietins	EU Similar biological medicinal products containing recombinant erythropoietins, EMEA/CHMP/BMWP/301636/2008 Rev.1
Biosimilar medicines containing recombinant follicle-stimulating hormone	EU Similar biological medicinal products containing recombinant follicle-stimulating hormone, CHMP/BMWP/671292/2010)
Biosimilar medicines containing somatropin	EU Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, EMEA/CHMP/BMWP/42832/2005 Rev. 1

5.1.5. Blood product

For all new biologic drug applications containing blood or plasma products, SFDA adopts the European medicinal agency guidelines for blood products including biotech alternatives.

5.1.6. Vaccine

For all new vaccine applications, please refer to clinical considerations for vaccines document at the SFDA website.

5.1.7. Generic drug

Generic drugs are products that are equivalent to the reference product in therapeutic indications, active ingredient, dosage form, strength, route of administration and quality characteristics. In case of changes to the active substance (e.g. different salt), additional information might be needed to exclude the effect of this change on the safety and efficacy of the generic product.

i) New generic drug of an SFDA registered reference product

For new generics of an SFDA registered reference, please refer to the GCC bioequivalence guideline on the SFDA website.

ii) New generic drug of a non-SFDA registered reference product

Applications of new generic products of a non-registered reference should include in addition to the bioequivalence requirements, a comprehensive literature review of the active substance to support the generic product registration. The literature review should be submitted in module 2.5 clinical overview and covers the following aspects:

- The search should be as extensive and relevant as possible
- The rationale for the development of the active substance as well as the generic product. The search should support the efficacy and safety of the active ingredient in each proposed indication.
- Bioequivalence and bioavailability data of the generic product.
- Safety and efficacy of the active substance in each of the proposed indications.
- Methodology of the search used should be stated in detail (database used, keywords used, and filters applied as well as date and time the search was carried on).
- Provide a tabular listing of the identified literature with their citations and arrange the studies according to the following:
    - Start with the key clinical studies (e.g. confirmatory studies).

- Well-designed, adequately powered, and preferably multicenter studies.
- Studies that have registered protocol or registered in clinical trials registries (provide registration status).
- Evidence from non-randomized controlled trials should be located in a separate section of the table.
- Post marketing safety studies.
- If possible, provide study reports for each identified study.

- Summarize 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).

5.2. Type II Variation Application: change(s) to therapeutic indication(s)

5.2.1. Variations to drug application and biological drug application

- **Addition of new therapeutic indication or modification of an approved one:**

Addition or modifications to the approved indications should be supported by data from a well conducted phase 2/3 clinical trial showing the safety and efficacy of the claimed indication/modification. Modification includes for example, addition of new age group, changes to the dosing regimen or expanding patient population. All relevant trial documents should be included as discussed in the new drug application section (Please refer to section 5.1).

- **Deletion of a therapeutic indication:**

In case of deletion of any indication, justification should be provided for the reason for deletion supported by clinical evidence if available.

5.2.2. Variations to generic and biosimilar drug application

Any variation of a product regarding therapeutic indications will not be considered unless approved for the reference product.