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Saudi Food & Drug Authority

General Guideline on Regulatory and Scientific Requirements for Development and Approval of Biosimilars

Version 1.0

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Saudi Food & Drug Authority

Drug Sector

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Saudi Food and Drug Authority

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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. Executive Summary

This guideline describes the general regulatory and scientific requirements for the development and approval of biosimilars. It provides a concise summary and discussion of the principle of biosimilarity and outlines the Saudi Food and Drug Authority (SFDA) current regulatory thinking and technical requirements for development and approval of biosimilars as embedded in the overall regulatory framework of SFDA (1). An overview is presented on the biosimilarity protocol, the choice of reference product (RP), and the concept of the biosimilar comparability exercise, including a new approach and conditions for waiving certain requirements that has developed over time based on the advancement of regulatory sciences and analytical technology coupled with a profound experience on the regulatory approval and use of biosimilars in clinical practice gained in recent years.

The guideline briefly addresses the regulatory requirements of the biosimilar comparability exercise for establishing biosimilarity at the quality, non-clinical and clinical levels, with cross-reference to specific, detailed SFDA guidance documents.Consideration is given on the aspects of extrapolation of indications, interchangeability and switching, which facilitate the availability, affordability and broad access of patients to an important group of biological medicines, the biosimilars.

This document is issued to provide guidance to stakeholders on the subject matter and does not create or confer any rights or obligations that are legally enforceable.

2. Introduction

A biosimilar is defined by SFDA as a biological product that is highly similar to an already approved reference product (RP) in terms of quality characteristics including structural and functional attributes and has no clinically meaningful differences (2). The RP is defined as innovative biological medicinal product – the so called originator, which is developed by biotechnology approaches, licensed by SFDA or stringent regulatory authority (SRA) on the basis of a full marketing authorization and marketed for a suitable period of time with proven quality, safety and efficacy. Many RPs have been introduced into the therapeutic armamentarium of modern medicine decades ago. Biosimilars are approved once the RP

becomes off-patent and regulatory exclusivity right is expired. Biosimilars are now being used on a global level to provide important and affordable therapeutic options for a wide variety of diseases, with the possibility of helping numerous patients, who otherwise would not have access to expensive innovative biological medicinal products.

Although specific legal provisions and regulations of biosimilars may slightly differ among jurisdictions globally, much progress has recently been made in efforts to harmonise the standards for development and approval of biosimilars (as exemplified in documents of the World Health Organisation (WHO) and the International Pharmaceutical Regulators Programme (IPRP), 3-4). On top of this generally accepted biosimilar regulatory framework, it is necessary for the support in development and approval of biosimilars to define certain regional provisions that regulate the generation and evaluation of scientific data needed for marketing authorisation in a given jurisdiction.

The regulatory and scientific requirements span the path of a biosimilar from manufacturing to biosimilar comparability excercises supporting biosimilar approval and to ensure quality, safety and efficacy after approval remain positive through the implementation of pharmacovigilance and post-approval surveillance activities.

At the heart of the biosimilar paradigm is the prerequisite of the biosimilar comparability exercise to demonstrate and confirm high similarity with no significant differences in the clinical performance compared to the RP. In consequence, it can be reliably assumed that patients will derive the same treatment benefit, with a highly similar profile of efficacy and safety, when receiving the biosimilar. This high similarity has to be demonstrated through various comparability exercises on several levels including the structural, functional and clinical outcomes of the biosimilar compared with the RP. While the analytical assays and results investigating the structural and functional characteristics have been substantially refined and improved in recent years, it has also been realised that the contribution of comparative clinical data, in particular the relatively insensitive comparative efficacy studies (CES) in patients, is quite limited and of questionable usefulness (5-8).

This regulatory evolution, which is summarised in the present general guideline, is now being recognised on a large scale and has the potential to advance the field of biosimilars,

with more efficient development at highest scientific rigor but lower expenditure in time and resources.

3. Scope and Purpose

This guideline addresses the general principles for the development and approval of biosimilars. It summarises on high level the regulatory and scientific considerations for establishing biosimilarity against the RP as the basis for submission of marketing authorisation applications of biosimilars. The guideline encompasses biosimilars containing active biological substance(s) produced by biotechnological processes, (e.g., well-characterized proteins and polypeptides). Parts of the principles may be applied to polysaccharides that are derived from biological sources, which are considered on a case-by-case basis. Other biological products such as blood products, vaccines, and advanced therapies, as well as synthetic peptides are excluded from the scope of this guideline.

The requirements for the comparability exercise addressing changes in the manufacturing process of products during development or after approval are not applicable to this guideline and are dealt with in other specific guidance documents, as outlined by ICH Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Processes Q5E (ICH Q5E; 9-10).

4. Biosimilarity Principle

The biosimilarity principle underlying the biosimilar pathway is to develop and approve a biosimilar containing a biological active substance highly similar in terms of quality characteristics including structural and functional attributes and with no clinically meaningful differences to an already approved RP (1). This implies that the efficacy and safety results previously established for the RP are also applicable to the biosimilar and there is no need to re-establish efficacy and safety per se for the biosimilar.

However, variability in individual biological molecules and between batches is inherent to all biological medicinal products including the RP and the biosimilar. Therefore, it is not possible to manufacture a biosimilar that would be identical to the RP, because of the use

of living organims and complexity of manufacturing process introducing heterogeneity in both the RP and the biosimilar.

The biosimilarity between the biosimilar and the RP must be demonstrated in a comparability exercise at all levels of quality characterisation, including structural and functional data, as well as clinical outcomes, including pharmacokinetics (PK), pharmacodynamics (PD), safety, immunogenicity and efficacy. For this purpose, a biosimilarity range of differences is pre-defined that would ensure the biosimilar to fall within the variability range derived from the characterisation of the RP and warrant the absence of any significant impact on clinical outcomes.

5. SFDA Regulatory Basis for Biosimilar Approval

The general concept of biosimilarity and other aspects of development and approval of biosimilars are laid down in this guideline, which should be read in conjunction with other technical and regulatory guidance documents published at the SFDA website, including:

- Regulatory Framework for Drugs Approval (1),
- Guideline on Quality Considerations for Development and Comparability Assessment of Biosimilars (2),
- Guideline for Bioequivalence (11),
- Regulations and Requirements for Conducting Clinical Trials on Drugs (12),
- Data Requirements for Human Drugs Submission (13),
- General Considerations for Preclinical Studies Submissions (14),
- Clinical Considerations for Efficacy and Safety Assessments (15),
- Guidance for Priority Review of Product Registration, (16), and
- Pricing Rules for Pharmaceutical Products (17).

Complete stand-alone Quality/Chemistry, Manufacturing, and Controls (CMC) data (Electronic Common Technical Document (eCTD) Quality Overall Summary of Module 2 and Module 3) should be provided in the submitted marketing authorization application (MAA) dossier, including information in the drug substance (DS) (3.2.S) and drug product (DP) (3.2.P) sections plus the Appendices (3.2.A) required for the characterisation of DS

and DP of the biosimilar, as detailed in the SFDA guidance "Data Requirements for Human Drugs Submission" (13). The submitted stand-alone Quality/CMC data should be supplemented with biosimilar comparability exercises on quality (eCTD Module 3; 3.2.R), non-clinical (eCTD Module 4) and clinical (eCTD Module 5) level where required to demonstrate the biosimilarity against the RP as discussed in the relevant guidelines (2, 14, 15, this guideline). The results of comparative non-clinical (*in vitro*) and comparative clinical studies are geared to complete the necessary evidence for biosimilarity with the RP.

From the quality perspective, a successful biosimilar comparability exercise requires several fundamental prerequisites, including:

- Extensive characterization of the structural and functional quality attributes of the RP and the biosimilar using orthogonal and state-of-the-art analytical methods,
- Comprehensive understanding of the mechanism of action of the active biological substance for the proposed biosimilar,
- A battery of functional *in vitro* assays to assess comparability of functional attributes,
- A validated manufacturing process and quality control strategy to ensure batch-to-batch consistency of the proposed biosimilar,
- A well-established and robust biosimilarity protocol, see section 5.1.

After the first authorization of a biosimilar, however, it becomes its own independent medicinal product. Like for other human medicines, pharmacovigilance of biosimilars is expected to follow the general obligations defined in the regulation of Good Pharmacovigilance Practice (18) and will in principle be oriented along any potential specific requirements as defined for the RP. For post-marketing variations there is no longer need to re-demonstrate biosimilarity to the RP. Rather, for modifications in e.g., manufacturing, presentation, or strength etc. in the post-approval phase, it will be necessary to demonstrate comparability between the biosimilar product before and after the respective change(s), see also the ICH Q5E guideline (9).

5.1. Biosimilarity Protocol

The biosimilarity protocol is essential for the overall robustness of the development and assessment of the biosimilar. A well designed and robust protocol as prerequisite prior to initiation of the pivotal biosimilar comparability exercise will facilitate and support a valid interpretation of the results and the conclusion on biosimilarity. The biosimilarity protocol should cover all critical parts that may impact the conclusion on biosimilarity, including:

- The selection of the RP should meet the SFDA requirements as defined in the SFDA Guidelines on Quality Considerations for Development and Comparability Assessment of Biosimilars (2), and as highlighted in section 5.2 in this guideline.
- The number of RP batches included in the comparative quality exercise (CQE) should be at least 15 batches and the sampling plan should account for batches with different ages. This condition will be considered by SFDA on a case-by-case basis for biosimilars of orphan medicines.
- The number of biosimilar batches included in the CQE should be sufficient (at least 10 batches) and should represent batches manufactured using the intended commercial process and scale. This condition will be considered by SFDA on a case-by-case basis for biosimilars of orphan medicines.
- Comprehensive risk assessment to identify critical quality attributes for functional attributes and clinical outcomes (PK/PD, safety/immunogenicity and efficacy) according to ICH guideline Q9 (R1) on quality risk management Step 5 (ICH Q9; 19) and ICH guideline Q10 on pharmaceutical quality system Step 5 (ICH Q10; 20).
- A clear definition along with justification for the proposed selected statistical approaches and biosimilarity acceptance criteria/range (for further details see the Guideline on Quality Considerations for Development and Comparability Assessment of Biosimilars (2).
- The analytical assays and methods should be qualified for use in the CQE.
- A detailed plan for handling differences between the proposed biosimilar and the RP.

- A comprehensive list of parameters to be captured in comparative PK/(PD) studies with comparability margins/limits for the main PK parameters defined and justified in the study protocol (for details see section 5.3.3. below).
- A justification letter for requesting the waiver of certain comparative clinical studies, in accordance with the conditions specified in this guideline.

Details for the required content of the biosimilar comparability exercise are provided in the relevant SFDA guidelines for biosimilars. However, companies developing biosimilars are invited to seek scientific advice from SFDA for further reassurance on the adequacy of their development program in line with the requirements for formal meeting between drug sector and applicants (21). This can be specifically valuable in cases where the available guidelines may not address a particular situation or a developer wants to deviate from the guidance for certain reasons to be justified, and when a tailored biosimilar approach with waiving of the CES in patients is pursued.

At presubmission stage it is strongly recommended that Applicants submit an outline of their biosimilar protocol to the agency for ensuring that only mature and complete dossiers meeting the standards for the design of the comparability exercise will proceed to the review stage. This interaction is not intended to provide a pre-assessment of the data, but rather prevents immature or inadequate dossiers lacking essential comparability results from being submitted, and thereby will enhance the efficiency of the evaluation process both for SFDA and the Applicant. A timeframe of at least 6 months before intended submission is foreseen for this interaction, in order to allow for sufficient opportunity to update the files.

5.2. Choice of Reference Product

The definition of the RP has been discussed in detail in the SFDA Guidelines on Quality Considerations for Development and Comparability Assessment of Biosimilars (2). In general, the selection of the RP should consider the following:

- The RP should have an expired patent and data exclusivity rights at the time of the marketing authorization for the biosimilar according to the SFDA policy for patent of pharmaceutical products (22).
- The RP has been approved by SFDA or SRA, on the basis of a full marketing authorization (1).
- The RP should have been marketed for suitable duration and patient experience in clinical practice and have a well-established safety and efficacy profile. This condition will be considered by SFDA on a case-by-case basis for biosimilars of orphan medicines.
- Selection of the RP coming from the Saudi market or SRA markets is required, as this guarantees experience of use in patients from Saudi Arabia or from regions overseen by SRAs (1).
- If more than one RP from different sources are employed throughout the various biosimilar comparability studies, the Applicant should use a single-sourced RP as main comparator throughout the biosimilar comparability exercise. It is the responsibility of the Applicant to scientifically justify that the data derived from one of the comparators is representative of the data from the other RP based on a bridging exercise demonstrating comparability of the RPs from different sources and the proposed biosimilar in a three-way comparison at the structural and functional level.
- The RP used throughout the development program must not be another biosimilar.

5.3. Biosimilar Comparability Exercises

The fundamental evidence for authorizing a biosimilar is derived from the biosimilar comparability exercises to demonstrate biosimilarity of the biosimilar compared to the chosen RP at all levels of product quality, biological activity, exposure, safety, immunogenicity and efficacy.

The type and extent of comparative data needed for demonstrating the requested high similarity has been refined by the experience gained over the past years ever since biosimilars have been licensed and used in the Kingdom of Saudi Arabia and on a global scale. While the sensitivity and explanatory power of analytical and functional assays have

been steadily improved, the experience over time with authorization and availability of numerous biosimilars has led to an evolution of the requirements for demonstration of biosimilarity at the non-clinical and clinical level. By contrast with the steadily enhanced quality data the sensitivity of clinical data, especially those from CES in patients, is lower, and although the demand for clinical evidence of biosimilarity has been globally supported by biosimilar regulatory frameworks, the need for CES in patients for all biosimilars has recently been discussed and challenged in a number of publications (e.g., 6-8). An important implication of these findings is that results from CES in patients, mainly thought to confirm the evidence of biosimilarity provided by the CQE, do not contribute significantly to the interpretation of biosimilarity and the conclusion for approval of biosimilars.

Thus, the demand for such CES in patients by default becomes increasingly questioned and should rather be requested on a case-by-case basis, after carefully taking into account specific characteristics, e.g., an unknown or poorly understood mechanism of action of RP, unclear structure-function relationship of critical quality attributes or differences in critical quality attributes between the proposed biosimilar and the RP that cannot be scientifically justified, a large extent of intrinsic complexity and heterogeneity of the molecule, analytical methods lacking sensitivity, novel impurities not observed previously or a high immunogenicity and local route of administration of RP rendering comparative PK/PD studies unfeasible. In most cases CQEs including structural and functional data together with results from PK/(PD) comparison could serve as proof of biosimilarity.

5.3.1.Comparative Quality Exercise

Details of the quality considerations relevant for the development and comparability assessment of biosimilars are discussed in the SFDA Guidelines on Quality Considerations for Development and Comparability Assessment of Biosimilars (2). In terms of the CQE, the same scientific principles apply as those given in the ICH Q5E guideline for evaluation of the impact of changes in the manufacturing process of a biological medicinal product (9).

Apart from data on DS and DP presenting a consistent manufacturing process with robust

process controls and well justified specifications, the dossier for MAA must contain a well-designed and acceptable biosimilarity protocol for comparability exercises along with the results of the CQE comparing structural and functional attributes (using *in vitro* assays) between the proposed biosimilar and the RP. Relevant and critical quality attributes should be predefined together with the chosen similarity condition and criteria, based on knowledge of the mechanism of action of the RP and structure-function relationships. State-of-the-art and orthogonal methods for analysis should be highly accurate, precise and sensitive, so that observed differences can be attributed to differences between the biosimilar and RP and not be due to variability or insensitivity of analytical methods.

5.3.2.Comparative Non-clinical (*In Vivo*) Studies

The non-clinical assessment of biosimilarity is generally performed with comparative *in vitro* assays investigating biological functions, as described in the Guidelines for Quality Considerations for Development and Comparability Assessment of Biosimilars (2), and included in Module 3 of the dossier for MAA. The extent and type of comparative non-clinical studies is determined based on the outcomes of CQEs. It is acknowleged that comparative *in vivo* studies are of limited use in the regulatory assessment of biosimilars due to their low sensitivity, high variability, species-specific or disease model-dependent differences with often minimal or absent relevance for the human pathophysiology and resulting lack of informative value. Therefore, these studies are normally not required for the evaluation of biosimilarity and, according to the principle of the 3Rs (replacement, reduction, refinement), are even not recommended.

Comparative non-clinical PK/PD and/or toxicological studies may only be required in exceptional cases including:

- Novel excipients without prior experience included in the formulation of the biosimilar,
- New critical quality attributes of the proposed biosimilar not detected in the RP,
- Novel impurities in the proposed biosimilar not detected in the RP.

If any comparative non-clinical *in vivo* animal studies appear necessary, these studies should be placed in Module 4. In all other cases the Applicant should provide a justification letter for not conducting comparative non-clinical *in vivo* studies using animal experiments.

5.3.3.Comparative Clinical Trials

The comparative clinical trials aim at demonstrating that no significant differences in exposure, safety, immunogencity, and efficacy exist between the biosimilar and the RP. This can in principle be deduced from the CQE substantiating high similarity in structure and function of the biosimilar with its RP along with comparative PK/(PD) trials.

Comparative pharmacokinetic/pharmacodynamic trials

Comparative PK/PD trials are an essential part of the comparative clinical exercise confirming biosimilarity and should mainly be conducted in healthy volunteers as the most sensitive population for detecting potential differences in PK, safety and immunogenicity between the biosimilar and the RP. However, in cases where ethical considerations related to the nature of the product (e.g., safety concerns) preclude this approach, the comparative clinical trial protocol should explicitly discuss this matter with the scientific justification needed.

Applicants should not rely on the label claim of the RP; instead, the extinction coefficient of the biosimilar and the RP should be experimentally determined early in the development in order to make an accurate determination of the true protein concentration, as slight differences between the proposed biosimilar and RP may lead to issues in demonstrating a comparable PK profile.

All relevant and critical PK endpoints, specifically, areas under the curves (AUCs), maximum plasma concentration (Cmax), the time needed to reach maximum plasma concentration (Tmax), terminal elimination half-life (T1/2), clearance and volume of distribution should be covered. The choice of PK endpoint, either primary or secondary, should be justified and discussed in detail, supported by evidence from literature related to the RP. The choice of design (crossover or parallel), sample size and dose (including for investigation of target-mediated and non-target-mediated clearance, if relevant) must be

justified in relation to the knowledge of the RP's PK profile. Using a three arms approach where the biosimilar is assessed in comparison with two RPs from different sources or a two arms approach where the assessment is with one sourced RP should be justified. Acceptance criteria for each endpoint should be clearly defined and discussed in the comparative clinical trial protocol with the necessary evidence to support the choice of equivalence margins.

In case of well-established PD endpoints/biomarkers that are associated with clinical efficacy, ideally specific for the mechanism of action, the design of the comparative study should include both PK and PD assessments, which helps to address minor quality differences, especially those related to the mechanism of action, providing further strength to the evidence of biosimilarity.

Comparative efficacy trials

Traditionally, the clinical development of biosimilars has also included a comparative efficacy exercise in patients, with focus on confirming comparable clinical performance and addressing residual uncertainty due to observed minor differences at the quality level. Despite some measures to increase the sensitivity of the CES (e.g., by selecting a most sensitive and homogeneous patient population, a most sensitive endpoint and timepoint for assessment) its responsivity for detecting differences remains lower than the highly sensitive comparison at the quality level and thus the necessity for CES in the overall regulatory decision as a mandate for all biosimilars has become a debatable requirement.

As also discussed above, this has led to considerations under which conditions the CES may be waived for biosimilar approval. A prerequisite for this tailored clinical approach is that a solid and robust biosimilarity conclusion based on the CQE demonstrating high similarity in structural and functional parameters coupled with a successful comparative PK (and PD if applicable) trial can be drawn. This implies that the biosimilar and the RP can be extensively characterised, that the mechanism of action and structure-function relationships of (critical) quality attributes are well understood and can be measured with sensitive, validated and qualified analytical methods, that conditions and criteria for biosimilarity are clearly predefined. Finally, the extent (AUC) and rate (Cmax and Tmax)

of systemic drug exposure should enable the conduct of a reliable PK comparison.

Comparative safety and immunogenicity data

Data on safety and immunogenicity are normally collected within the CES. In case of waiving the CES in patients, appropriate measures should be taken and scientifically justified to gather sufficient information for comparing the safety and immunogenicity profile from comparative PK trials, by possibly increasing the sample size, study duration or number of administrations. The immunogencity profile of the RP should be considered, including the temporal pattern of antibody formation, potential cross-reactivity with endogenous ligands and clinical consequences.

Biologic medicines, by their nature as complex molecules (such as proteins, nucleic acids, sugars, cells, or tissues) derived from living organisms, have the potential to elicit an immune response, leading to the formation of anti-drug antibodies (ADAs). Immunogenicity assessment is a critical part in the development and approval of biosimilars, as it directly impacts patient safety and treatment efficacy. Whenever no CES is conducted, the assessment of PK and PD must always include immunogenicity assessment. If ADAs are known to significantly impact efficacy or safety over time, immunogenicity data from a single-dose PK study may be insufficient. In such cases, multiple doses may be needed to properly assess immune response, ideally in a suitable immunocompetent population (healthy volunteers or patients). The assessment should include quantification and characterization of ADAs including neutralizing antibodies (NAbs) at specific justified preplanned timepoints using validated assays.

Safety assessment in terms of immediate reactions and adverse events throughout the course of the study should also be part of the design in such cases. However, it is important to acknowledge that such safety assessment is limited and may not be able to capture certain rare immunogenic reactions that do not alter PK but could result in adverse events.

6. Conditions for Waiving Comparative Efficacy Studies

Taken together, when a biosimilar's comprehensive CQE demonstrates high similarity and high purity compared to the RP, a well-defined set of comparative safety and immunogenicity data as part of the PK study may be enough to ensure confidence in its safety and immunogenicity profile in the absence of a CES.

Based on an SFDA internal analysis of all approved and rejected biosimilar applications submitted to the SFDA prior to the issuance of this guidance, no cases were identified in which a product demonstrated a positive outcome in the CQE while exhibiting a negative outcome in the comparative clinical trial. Despite this analysis being limited by the number and types of biosimilars included, this observation supports SFDA's position that a robust and comprehensive demonstration of biosimilarity at the quality level is predictive of comparable clinical performance. Consequently, this finding reinforces the scientific rationale for waiving CESs in certain biosimilar applications except in the following conditions:

- If the function of RP has unknow or poorly understood mechanism of action, then CESs will be required.
- If the structure of RP can not be sufficiently characterized due to complexity and heterogeneity of biological molecule.
- If differences in critical quality attributes between the RP and proposed biosimilar cannot be scientifically justified.
- If safety and immunogenicity cannot be demonstrated from the comparative PK trial, e.g., due to a high immunogenic risk of RP or locally administered RP, a CESs in patients may eventually become necessary in addition to other evidence (e.g., a population PK approach of drug concentration together with ADA detection).
- See Annex 1 for more information on factors to be considered for waiving comparative efficacy studies.

7. Extrapolation of Indication

Most biological medicinal products have more than one therapeutic indication. When biosimilarity has been demonstrated for one indication, extrapolation to other indications of the RP should be accepted with proper scientific justification and in compliance with the SFDA policy on patent for pharmaceutical products (22).

Biosimilarity based on the totality of comparative quality, non-clinical and clinical data, demonstrated by thorough physicochemical and structural analyses, *in vitro* functional tests and complemented with comparative clinical data, allows to extrapolate the safety and efficacy results. Critical factors to be taken into consideration are the mechanism of action of the active biological substance in the various authorized indications of the RP, as well as the pathogenic mechanisms shared by the disorders reflected in these therapeutic indications, and the immunogenicity of the RP.

Additional data from the CQE to compare functional attributes using a battery of *in vitro* assays (including e.g. comparative assessment of Fc receptor binding and function such as Antibody-Dependent Cell-mediated Cytotoxicity - ADCC, Complement-Dependent Cytotoxicity - CDC, Antibody-Dependent Cellular Phagocytosis - ADCP) are required to implement extrapolation in cases where the mechanism of action of the RP varies by

- Interacting with several receptors that may have a different impact in the tested and non-tested therapeutic indications or by
- Operating through more than one active sites which may have a different impact in different therapeutic indications.

Another situation necessitating more data to specifically justify extrapolation arises when one therapeutic indication of the RP is not relevant for the others in terms of efficacy or safety, e.g., when intracellular signal transduction pathways vary (such as for depletion of immune cells) or immunogenicity differs due to co-medication, nature of the disease (autoimmune versus oncological) or immune status of patients. The type and amount of supportive results needed can often be obtained from further comparative functional *in vitro* experiments, but might also include comparative clinical investigations (e.g., in

comparative PK/(PD) studies). In some of these cases, waiving of the CES from the overall biosimilar comparability exercise may not be possible or may require a comparative clinical trial for those specific indications affected by such factors to be included in the approved label.

Another reason for divergence in granting all therapeutic indications approved for the RP to the biosimilar might be due to patent protection as well as the choice by the biosimilar Applicant not to market all dose strengths/presentations available for the RP.

8. Interchangeability

Interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. Once a biosimilar is approved according to the stringent regulatory standards as implemented by the SFDA and by other reference regulatory agencies following the same rigorous scientific norms, it is considered interchangeable. This means that the biosimilar can be used with the same therapeutic intent instead of its RP (or vice versa), because based on the high similarity established for the biosimilar the efficacy and safety results previously obtained for the RP can be assigned to the biosimilar. It furthermore follows that there is no demand for additional systematic switch studies post-authorisation to support interchangeability.

Interchanging of medication can either be implemented through switching, which means it occurs with knowledge and under the control of the prescriber, or by means of (automatic) substitution, where one medicine is dispensed in the pharmacy instead of another medicine without consultation of the prescriber. The latter is mainly practiced in health care systems with tenders, where certain medications are bought at large scale and best price for the institutional provider.

Experience with more than 100 biosimilars approved in the EU and more than one million patient-treatment years shows that biosimilars are safe and can be used interchangeably, without any negative impact on efficacy, safety or immunogenicity (23). In addition, SFDA's pharmacovigilance system identified no reporting of safety concerns specific to biosimilars after approval. An internal immunogenicity analysis of available switching

studies for biosimilars approved by SFDA revealed no significant differences in ADA and NAb development following switching. Despite the limited data of this analysis, these findings support the notion that immunogenicity is not a concern with respect to the overall interchangeability between biosimilars and their RPs and that the absence of such switching studies does not contradict the overall scientific consensus on biosimilars being interchangeable with their RPs.

This is further substantiated by a recent systematic review and meta-analysis assessing the safety of switching from RP to biosimilars. The analysis, which included 12 trials with over 2,500 participants, found no significant differences in the incidence of adverse events, serious adverse events, or treatment-related adverse events between patients who remained on the RP and those who switched to a biosimilar. These findings provide additional reassurance regarding the safety of switching and support the scientific justification for interchangeability without the need for further dedicated switch studies (24).

Notwithstanding, as this interchangeability in principle relates to the active substance, it should only take place after careful consideration of the approved conditions of use as indicated in the product information, accounting for potential differences in e.g., excipients which might entail different precautions for use (25).

9. Request for Waiver of Requirements

Applicants may request a waiver of unessasary comparative clinical studies which will be evaluated by SFDA on case-by-case basis. Such requests must fullfil the following requirements:

i. Compliance with Applicable Requirements and Conditions

The waiver request shall demonstrate compliance with requirments in this guideline and fullfill the conditions in Section 6. Any request that fails to meet the applicable requirements or conditions would be rejected. The SFDA‘s recommendation on waiver of requirments is not legally binding consultaion on either the applicant (medicine developer) or the SFDA. It is a proactive, consultative process intended to provide guidance on

development strategies and does not constitute a pre-evaluation or guarantee of future marketing authorization approval.

ii. Required Documents

1. Request Form

The applicant should be the MAH of the proposed biosimilar and it must provide all applicable information in the form (Annex 2). Providing incomplete, inaccurate, or missing information would lead to rejection of request.

2. Justification Letter & Supportive data

The applicant shall provide a comprehensive justification letter explicitly specifying the clinical studies for which a waiver is sought. The justification should be supported by adequate scientific data and evidence, including the biosimilarity assessment protocol and any relevant quality, non-clinical, or clinical comparability data.

iii. Submission Process

The waiver request, including all required documents, should be submitted to the SFDA via the following email:

SDR@sfda.gov.sa

iv. Evaluation Timeline

The applicant will receive an official response within 60 working days from the date of submission. During the review period of the waiver rquest, the SFDA may request additional information or schedule a meeting with the applicant if deemed necessary.

10. Abbreviations

ADA	Anti-Drug Antibodies
AUC	Area Under the (Plasma Concentration) Curve
CES	Comparative Efficacy Studies
Cmax	Maximum Plasma Concentration
CMC	Chemistry, Manufacturing, and Controls
CQE	Comparative Quality Exercise
eCTD	Electronic Common Technical Document
DP	Drug Product
DS	Drug Substance
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IPRP	International Pharmaceutical Regulators Programme
MAA	Marketing Authorization Application
Nab	Neutralizing antibodies
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
RP	Reference Product
SFDA	Saudi Food and Drug Authority
Tmax	Time to Maximum Plasma Concentration
T1/2	Terminal Elimination Half-life
US	United States
WHO	World Health Organization

11. Glossary

Anti-drug antibodies: antibodies produced by the recipient body specifically against the therapeutic biologic drug.

Bioequivalence: absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Biological activity: specific ability or capacity of the product to achieve a defined biological effect.

Biological product: medicinal product mainly based on biotechnology-derived proteins, mostly for recombinant DNA-derived versions. Other terms are biological medicinal product or biologic.

Biosimilar: a biological product highly similar to an already approved reference product in terms of quality characteristics including structural and functional attributes and has no clinically meaningful differences.

Biosimilarity: absence of any relevant difference in the parameter(s) of interest.

Biosimilar comparability exercise: direct head-to-head comparison of a biological product with a licensed reference product with the goal of establishing similarity in quality, safety and efficacy through analytical, preclinical, and clinical studies.

Biosimilarity range: predefined acceptable range for biosimilarity in each of structural and functional quality attributes when comparing the biosimilar to the reference product.

Comparability margin: the largest differences in quality attributes, preclinical results, and clinical data that can be judged as being clinically acceptable.

Comparative efficacy study: the clinical trial that is designed to compare the efficacy (and safety) of the biosimilar product and the reference product.

Comparative quality exercise: The analytical study conducted with the biosimilar product and the reference product to compare their structural and functional quality attributes.

Critical quality attribute: A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the

desired product quality. These are attributes that determined to be critical based on risk assessment, which are most important to be carefully assessed during comparative quality exercise.

Drug product: a pharmaceutical product that typically consists of a drug substance formulated with excipients.

Drug substance: The downstream-purified material which is subsequently formulated with excipients to produce the drug product. It can be composed of the desired product, product-related substances, and product- and process-related impurities. It may also contain excipients including other components such as buffers.

Equivalent: equal or highly similar in the parameter of interest. Equivalent quality, safety and efficacy of two medicinal products denotes that they can be expected to have similar (no better and no worse) quality, safety and efficacy, and that any observed differences are of no clinical relevance.

Excipient: a constituent of a medicine other than the drug substance, added in the formulation for a specific purpose. While most excipients are considered inactive, some can have a known action or effect in certain circumstances (for example, hyaluronidase or polysorbate). The excipients may differ for a biosimilar and its reference product. The excipients need to be declared in the labelling and package leaflet of the medicine to ensure its safe use.

Extrapolation: a regulatory principle that allows a biosimilar drug to be approved for use in additional medical indications that were not directly studied in comparative clinical trials, based on the totality of evidence demonstrating it is highly similar to the originator biological product in terms of quality, safety, and efficacy.

Immunogenicity: the ability of a biological moiety to trigger an immune response, e.g., development of anti-drug antibodies, neutralizing antibodies, antibodies to process impurities (e.g., host cell proteins), or to trigger a physiological reaction (e.g., T-cell response, or allergic or anaphylactic reaction). Immunogenicity of a therapeutic biological product (including a monoclonal antibodies) is undesired, and differs from desired immunological properties of monoclonal antibodies.

Impurity: any component present in the drug substance or drug product that is not the desired product, a product-related substance or excipient (including buffer components). Impurities may be either process or product related.

Interchangeability: the reference medicine can be replaced by a biosimilar (or in reverse) without a patient experiencing any changes in the clinical effect.

Neutralizing antibodies: a subset of anti-drug antibodies that bind to the drug and inhibit its pharmacological function by preventing target binding

Originator product: a medicine that has been licensed by a National Regulatory Authority on the basis of a full registration dossier – that is, the approved indication(s) for use were granted on the basis of full quality, efficacy and safety data.

Pharmacodynamics: the study of biochemical, physiologic, and molecular effects of drugs on the body.

Pharmacokinetics: the study of how the body interacts with administered drugs for the entire duration of exposure, comprising the four stages of absorption, distribution, metabolism, and excretion.

Pharmacovigilance: the science and activities relating to the collection, detection, assessment, monitoring, and prevention of adverse effects of pharmaceutical products.

Process-related impurities: impurities in a biological product that are derived from the manufacturing process. They may be derived from cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or downstream processing (e.g., processing reagents or column leachables).

Product-related impurities and degradants: molecular variants of the desired biological product (e.g., precursors, certain degradation products arising during manufacture and/or storage) which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety.

Quality attribute: structural and functional characteristics of drug substance or drug product that can be measured analytically, such as product-related substances, product-related impurities, process-related impurities, and contaminants. They include both critical and noncritical quality attributes.

Quality risk management: a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

Reference product: a biological product used as the comparator in a direct head-to-head comparability exercise with a biosimilar in order to demonstrate similarity in terms of quality, safety and efficacy. Only an originator product licensed on the basis of a full registration dossier and marketed for a suitable period of time with proven quality, safety and efficacy can serve as a reference product.

Switching studies: are designed to compare the outcomes in patients who alternate between the reference product and the biosimilar (who switch) to those who do not, with the goal of demonstrating that such switches have no negative impact on patients' safety or on treatment effectiveness.

3Rs: the pinciple of Replacement, Reduction, and Refinement in animal research aims to minimize animal suffering and promote ethical animal research by using non-animal alternatives (replace), using the fewest animals necessary (reduce), and modifying experimental conditions to minimize pain and distress for the animals (refine).

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13. Annex 1: Factors to be considered for waiving comparative efficacy studies

		Evaluation factors	Action Plan*
Quality aspects	**Biosimilarity Plan**	The biosimilarity protocol Is robust and meet regulatory requirement?	**If No,** revisiting the development program to establish a robust biosimilarity plan meeting regulatory requirements is required. **If Yes,** waiving CES may be considered if all factors addressed**.**
	Characterization	Is the product well-characterized at a high-level in terms of structure and function? Is the analytical method qualified and fit-for-purpose?	**If No,** if additional characterization studies are insufficient to resolve scientific uncertainty, CES or other development pathways may be considered. **If Yes,** waiving CES may be considered if all factors addressed
		Is the mechanism of action (MoA) well understood for all known indications, and have all critical quality attributes (CQAs) that influence the MoA been identified?	**If No,** further studies (e.g., nonclinical, PK, etc.) to resolve uncertainty in the MoA and CQA should be conducted first, and conducting CES may be useful. **If Yes,** waiving CES may be considered if all factors addressed
		Is the structure-activity relationship (SAR) well-known and established?	**If No,** sscientific uncertainties can usually be resolved through in-depth additional studies (e.g., cell-based biological assays reflecting the MoA). If uncertainties still remain, CES may be useful. **If Yes,** waiving CES may be considered if all factors addressed
		Can the potential differences in some quality attributes (QAs) between the reference product (RP) and the proposed biosimilar (BS) adequately explain their potential impact and significance on the safety and efficacy of the final product when administered to patients?	
	Manufacturer	Is the product manufactured on a stable process platform with	**If No**, revisiting of manufacturing process to further improvement is required. CES cannot rescue

		well-established process studies capable of ensuring quality consistency over time and across multiple manufacturing process changes?	unstable and inconsistent manufacturing process. **If Yes,** waiving CES may be considered if all factors addressed
	Assay	Are there well-established analytical and biological assays sensitive enough to detect differences between the RP and proposed BS in terms of QAs? Do the biological assays reflecting the MoA (e.g., cell-based assays) and possess adequate precision, accuracy, and sensitivity?	**If No,** if analytical and biological assays cannot be further improved in terms of sensitivity, precision and accuracy, CES may be required or other development pathways may be considered. **If Yes,** waiving CES may be considered if all factors addressed
Clinical aspects	**Pharmacokinetic (PK)**	Is it possible to assess the PK of systemic exposure? (for example, for locally applied products, assessing systemic exposure PK may generally be difficult)	**If No**, clinical models that can sensitively assess exposure-response differences, such as CES, may be useful as an alternative to assessing systemic exposure PK. **If Yes,** waiving CES may be considered if all factors addressed
	Pharmacodynamic (PD)	A valid PD biomarker is available?	**If No**, if comprehensive analytical and functional characterization and comparison of PK demonstrate biosimilarity, measurement of a valid PD biomarker may not be essential, but other PD parameters could yield supportive information. **If Yes,** waiving CES may be considered if all factors addressed
	Immunogenicity	Does the RP information suggest that immunogenicity will not impact efficacy (e.g., neutralizing antibodies)	**If No,** aadditional comparative immunogenicity assessments are

		or safety (e.g., serious injection reactions)?	necessary, and conducting CES may be a useful measure.
		Are ccomparative quality exercise and/or comparative pharmacokinetic studies designed to assess the potential risk of immunogenicity?	**If Yes,** waiving CES may be considered if all factors addressed

***** Please note that these examples given are considered relevant in general, but cannot cover all individual situations, which need to be assessed by SFDA on case-by-case basis depending on the totality of available data.

14. Annex 2: Request Form

A. Applicant information
• Applicant Name: • Address: • Contact Information:
B. Product information
• Type of product: *e.g.: monoclonal antibody, recombinant enzyme, etc* • Stage of development: • Development code: • Trade name: • Scientific name: • Regulatory status in stringent regulatory authorities[1]: • Dosage form: • Indication(s): • Anatomical Therapeutic Chemical (ATC) code:

[1] Refere to SFDA Regulatory Framework for Drugs Approval for more information regarding stringent regulatory authority.

C. Waiving Request information
• Type of studies intended for waiver: • Have you previously submitted a waiver request? □ Yes □ No If yes, please provide the justification for submitting a new request:
D. Required documents
• Information on biosimilarity protocol will be submitted with the request? □ Yes □ No • Justification letter and supporting data will be submitted with the request? □ Yes □ No If no, please provide the justification for not submitting the required documents:
E. Applicant signature
☐ I confirm and acknowledge the information mentioned above. ☐ I acknowledge that the decision on this request is not legally binding to SFDA nor Applicant. ☐ I consent not to misuse any information that would be provided by SFDA in the future. ☐ I consent to release SFDA from any demands, claims and liabilities arising out of or related to any loss, damage, or risks that may be sustained by the company in the future. Name: Job title: Signature: Date of request: