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Saudi Food & Drug Authority

Guideline on Quality Considerations for Development and Comparability Assessment of Biosimilars

Version 2.0

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Saudi Food & Drug Authority

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Saudi Food and Drug Authority

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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
1.0	Executive Directorate of Products Evaluation	22 August 2017	Final
2.0	Executive Directorate of Quality Evaluation of Medicines	17 June 2025	Update (Implementation date 17 August 2025)

What is New in version no. 2.0 ?

The following table shows the update to the previous version:

Section	Description of change
Scope and Purpose	**Update:** Clarification on the type of biological products falling within and out of the scope of this guideline.
SFDA Regulatory Basis of Review and Approval	**Add:** 4.1 Biosimilar Quality/Chemistry Manufacturing Control data. 4.4 Extrapolation of Indication. **Update:** 4.2 Comparative quality exercise between the biosimilar and the reference product. 4.3 Definition of the Reference Product.
Biosimilar Development Paradigm: Stepwise and Tailored Approach	**Add:** 5.1.2 Quality Target Product Profile. 5.1.3 Drug Substance of Biosimilar. 5.1.4 Drug Product of Biosimilar. 5.1.5 Analytical Test Methods for Biosimilar. 5.2.5 Comparative Stability and Degradation. 5.2.6 Selection and Identification of Batches of Reference Product and the Biosimilar. 5.2.7 Use of Official Biological Product Reference Standards. 5.2.9 Statistical Approaches. **Update:** 5.1.6 Specification of Biosimilar. 5.2.1 Comparative Physicochemical Properties. 5.2.2 Comparative Biological Activity. 5.2.3 Comparative Purity and Impurities. 5.2.4 Comparative Quantity. 5.2.8 Analytical Method consideration.
Glossary	**Add:** Table for glossary.

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ABBREVIATIONS

ADCC	Antibody-Dependent Cellular Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
BS	Biosimilar
CQE	Comparative Quality Exercise
CDC	Complement-Dependent Cytotoxicity
CHO	Chinese Hamster Ovary
Quality/CMC	Quality/Chemistry, Manufacturing, and Controls
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
C1q	Complement Component 1q
eCTD	Electronic Common Technical Document
DS	Drug Substance
DP	Drug Product
Fc	Fragment Crystallizable
GMP	Good Manufacturing Practice
HCP	Host Cell Proteins
HC DNA	Host Cell DNA
ICH	International Conference on Harmonization
KPP	Key Process Parameter
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
mAbs	Monoclonal Antibodies
MOA	Mechanism of Action
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
Ph. Eur.	European Pharmacopoeia
QA	Quality Attribute
QTPP	Quality Target Product Profile
RA	Risk Assessment
RP	Reference Product
SD	Standard Deviation
SFDA	Saudi Food and Drug Authority
USP	United States Pharmacopeia
WHO	World Health Organization

1. Executive Summary

This guideline provides updates and clarification on the regulatory requirements for development and approval of biosimilars. This update is triggered by the advancement in science and technology and regulatory experiences on biosimilar regulation. [1,2] In addition, this update reflects the regional regulatory requirements set by SFDA to promote patient-accesses to biosimilars and to achieve the goals of the national biotechnology strategy through localization of biosimilar industry in the Kingdome of Saudi Arabia.

The guideline lays down the Quality/ Quality/Chemistry, Manufacturing, and Control (Quality/CMC) considerations of the regulatory requirements for new marketing authorization applications (MAA) of a biosimilar (BS). This guideline addresses expected steps to be performed during BS process and product development to submit complete standalone Quality/CMC data for the Drug Substance (DS) and Drug Product (DP) of the BS and comparative quality exercise (CQE) in the electronic common technical document (eCTD). This Quality/CMC data should be included in the Quality Overall Summary of Module 2 and full Module 3 of the MAA dossier.

The guideline also describes the BS development pathway, the design of the CQE and the quality and methodological aspects to be considered during the CQE, including but not limited to the selection of RP batches, analytical methods, and statistical approaches for establishing acceptance criteria. Results from the CQE are an additional regulatory and quality element to be summited in Module 2 and Module 3 (3.2.R) in the MAA dossier of BS.

2. Introduction

The regulatory pathway for the approval of small molecule generic is well established in most countries.[3] Demonstration of structural sameness and bioequivalence of the generic and the RP is usually sufficient for therapeutic equivalence between the generic and RP to be inferred.

However, the regulatory pathway of generics is not suitable for the regulatory approval of BS because they consist of large, complex macromolecules that are orders of magnitude bigger than most small molecule pharmaceuticals. In addition, BSs are biopharmaceutical products that are produced from living organisms using recombinant DNA technology through a complex biomanufacturing processes, and typically require specific formulation components and storage

conditions to maintain their stability.[4] Moreover, biopharmaceutical products including RP and BS can trigger immunogenicity responses in patients, which could potentially affect safety and efficacy of biologically-based therapeutic products.[5]

Many biopharmaceutical products can be well-characterized with an appropriate set of state of the art and orthogonal analytical methodologies to define their quality attributes (QAs) including physical, chemical, microbiological, and biological properties.[6,7] Most biopharmaceutical products have a degree of molecular heterogeneity that are inherent to the process and the product. Changes in production processes of biopharmaceutical products might yield some minor differences in QAs, which are often not clinically meaningful means that they pose no increased risk to safety and provide suitable efficacy to their original production processes.[8]

A BS is manufactured by biotechnology-based approaches via different manufacturing processes following the patent expiration of the RP, which has been granted a marketing authorization based on a complete registration dossier submitted by the originator company.[3] Therefore, the BS is defined as a biopharmaceutical product highly similar to an already approved RP in terms of quality characteristics including structural and functional attributes and has no clinically meaningful differences.

Just like manufacturers of the original RP, manufacturers of BS should demonstrate a full understanding of their manufacturing processes for bulk DS and formulated, filled DP. They should have an appropriate quality control strategy to assure consistent, robust manufacturing and stability of DS and DP for the BS.

3. Scope and Purpose

The guideline provides information for MAA applicant of biosimilars to highlight regulatory considerations for the development of BS and the CQE required to establish the biosimilarity against the RP.

The guideline applies to biopharmaceutical products that can be well defined and analytically characterized, such as polypeptides and proteins produced by biotechnology-based approaches. Parts of the principle may be applied to polysaccharides that are produced via biotechnology

process, which are considered on a case-by-case basis. Vaccines and human plasma-derived products, animal tissue-derived products are excluded from the scope of this guideline.

This guideline does not address the comparability exercise for changes introduced in the quality control and manufacturing process of a given product (i.e. changes during development and post-authorization) as outlined by ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Processes (ICHQ5E).[9]

This guideline does not address safety and efficacy considerations for regulatory approval of BSs.

4. SFDA Regulatory Basis of Review and Approval

4.1.Biosimilar Quality/Chemistry Manufacturing Control data

A complete standalone Quality/CMC data (eCTD Quality Overall Summary of Module 2 and Module 3) should be provided in the submitted MAA dossier, including information on the DS (3.2.S) and DP (3.2.P.) sections plus the Appendices (3.2.A) is required for the DS and DP of the BS, as detailed in the SFDA guidance "Data Requirements for Human Drugs Submission".[10] The submitted standalone Quality/CMC data should be supplemented with CQE data demonstrating the comparability of BS with the RP (eCTD Module 3; 3.2.R), as discussed in this guideline. [11]

4.2.Comparative Quality Exercise between the Reference Product and the Biosimilar

The data generated in the CQE comparing the BS to the RP should be presented and discussed separately in section 3.2.R of Module 3. The submitted CQE data should be presented completely and clearly such that structural and functional similarity of the BS to the RP can be definitively compared and evaluated. In order to represent the quality profile of the BS batches to be commercialized, it is strongly recommended to generate the required CQE data for the demonstration of biosimilarity against the RP using BS batches that have been manufactured with the intended commercial manufacturing process.

The totality of data provided in the CQE is the basis on which the SFDA determines the amount of head-to-head/ comparative preclinical and clinical data needed to confirm that any minor differences in the BS will not negatively impact clinical outcomes relative to the RP. The type and extent of necessary comparative preclinical and clinical data will depend on prior knowledge of general biological product quality characteristics, the potential immunogenicity from biological

impurities, the Mechanism of Action (MoA) of the RP product, the results and remaining uncertainties from the CQE, and the clinical experience of safety (including immunogenicity) and efficacy with the RP with its DP presentation in the intended patient population. The nature and extent of comparative preclinical or clinical program is considered by SFDA on a case-by-case basis, the applicant should consult the SFDA guideline on clinical considerations for efficacy and safety assessment. [12]

Once the SFDA grants marketing authorization for the BS, a BS company may independently introduce its own post-approval DS or DP manufacturing changes according to the ICHQ5E and following the appropriate post-approval change regulatory requirements. SFDA regulatory authorization for post-approval changes in a BS does not require re-demonstration of biosimilarity against the RP. All post-approval DS or DP manufacturing changes should be submitted according to SFDA guidelines for variation requirements. [13]

4.3.Definition of the Reference Product

Comprehensive information on the RP provides the basis for establishing the quality, safety, and efficacy profile to gauge the comparability of the BS against the RP. The RP selected for use in the CQE should have the same dose and route of administration as the proposed BS.

For the MAA of a specific BS, a single original RP from one marketing authorization holder (MAH) should be defined and selected to allow the generation of coherent data and conclusions from the CQE. An approved BS from another MAH cannot be used as the RP for the development and approval of a new BS.

It is acknowledged that the use of locally registered RP may not always be feasible. As such, the use of non-locally registered RP may be allowed to enable faster development of and access to important and affordable biopharmaceutical therapies. Therefore, the use of an RP sourced from another jurisdiction with similar scientific and regulatory standards to SFDA may be allowed on a case-by-case basis by SFDA.

The selection of the RP depends on the registration status of the RP, the availability of the RP in the local market, the location of the manufacturing site of the BS. Since the selection of the RP is critical in the development and approval of a BS, the following points should be considered:

- The RP should have an expired patent and data exclusivity rights at the time of the marketing authorization for the BS according to the SFDA policy for patent of pharmaceutical products (access to https://www.sfda.gov.sa/ar/regulations/87572).

- The RP should be an originator product that has been approved by SFDA or its reference regulatory agencies, on the basis of a full standalone MAA that includes Quality, preclinical, and clinical safety and efficacy data. Consult SFDA regulatory framework for information on the reference regulatory agencies.[14]

- The RP should have been marketed for suitable duration and patient experience in clinical practice and have well established safety and efficacy profile. This condition will be considered by SFDA on a case-by-case basis for BS of orphan medicines.

- If a BS will be locally manufactured, the selection of the RP is determined based on the development approach of the proposed BS. The BS is considered locally manufactured if full of biomanufacturing process including upstream and downstream step(s) are conducted in the kingdom of Saudi Arabia. A Typical biomanufacturing involves the following steps establishing and maintenance of cell line and cell banks, cell culture and/or fermentation, isolation, purification, modifications, formulation, and filling in the primary packaging.[15] The secondary packaging only shall not qualify a BS to be considered a locally manufactured.

    - If a full development of the BS from DS to DP is conducted locally, the RP from the local market should be used as main comparator, if feasible.

    - If a partial development of the BS is intended to be based on the DS or DP processes included in a current MAA for the same BS, where either the DS or DP part(s) of the BS manufacturing process is technology transferred to a local new manufacturing site, the RP from the market of one of the SFDA reference agencies should be used as the main comparator, if a CQE is required. In this case, a technology transfer plan for the

designated DS or DP process, including a process comparability study according to ICHQ5E between batches from the transferring and receiving manufacturing site, should be clearly identified in the MAA dossier (e.g., Section 3.2.S.2.6 for DS process and 3.2.P.2.3 for DP process). The need of CQE with a comparator RP required after technology transfer of the BS DS or DP processes will be considered on a case-by-case basis, because it depends on the nature and extent of step(s) and manufacturing activities of the BS processes that will be transferred.

- Note that a partial development of a BS based on leveraging or referencing DS or DP processes described in a different MAA dossier of already approved BS is not accepted by SFDA because BS, like all biopharmaceutical products, require complete Quality/CMC data (Module 3) on the development and control of the DS and DP manufacturing processes to ensure process consistency and product quality, safety and efficacy throughout lifecycle.

- if a BS is not to be locally manufactured, it may be possible to use the RP(s) sourced from foreign markets (non-local RP) if the following conditions are met:

  - The non-local RP should be derived from a market under regulation of SFDA's reference agency(ies) (e.g., EMA and US FDA), which have a well-established regulatory framework and post-approval surveillance system, and extensive experience with the evaluation of biological products and biosimilars; and

  - The use of non-local RP(s) in the comparative (head-to-head) preclinical and clinical studies requires CQE bridging studies where the RP sourced from the market of SFDA's reference agencies, and the market of biosimilar developer are compared at quality level to demonstrate that the non-local RP(s) represent the RP from the reference and local market and the market of biosimilar developer; and

  - If the local RP and non-local RP(s) have different formulation that may affect the PK/PD profile, additional comparative PK and/ or PD studies may be required. In this

case the MAA applicant should also consult the SFDA guideline on Clinical Considerations for Efficacy and Safety Assessment. [12]

- If the RP is not available in Saudi market, it is important to note that the SFDA acceptance of a non-locally registered RP for the BS comparability exercise does not mean the SFDA has approved the RP for use in Saudi market after acceptance of the BS.

4.4.Extrapolation of Indication

For the RP with multiple indications, the SFDA may extrapolate the approval to indications other than those investigated in comparative clinical trials to the BS under the following conditions are fulfilled:

- The result of the CQE confirms high similarity in Quality Attributes (QAs), specifically the Critical Quality Attributes (CQAs), using sensitive and orthogonal assays to assess structural and functional attributes, which provide information on the clinically relevant MoA and/or involved receptors. The MoA must be similar across all indications for which extrapolation is sought

- The result of comparative preclinical *in vitro* and clinical trials (including comparative PK/PD study preferably on healthy volunteers and comparative efficacy trial in sensitive patient population for one therapeutic indication) support the results of CQE and confirms clinical equivalence to the RP according to the SFDA guideline on Clinical Considerations for Efficacy and Safety Assessment. [12]

5. Biosimilar Development Paradigm: Stepwise and Tailored Approach

The development and comparability exercises of the BS should follow a stepwise and tailored approach.

a) “Stepwise” refers to the development of the BS that starts with extensive characterization of the RP to develop a quality target product profile (QTPP) that guides the design of BS manufacturing process, which is followed by comparability exercises.

b) "Tailored" refers to the extent of three-tiered comparability exercises required to support BS approval. The first-tier comparability exercise comprises the CQE to establish and demonstrate molecular biosimilarity, the second tier comprises the comparative (head-to-head) PK/PD studies, and the third tier is the comparative clinical data needed to confirm high similarity of the safety and efficacy of the BS as compared to the RP.

5.1.Considerations for Biosimilar Development

5.1.1. Quality Target Product Profile

The manufacturer developing a BS normally have no access to the detailed technical information on the Quality/CMC data of the RP counterparts including the DS and DP. Therefore, the first step in the BS development starts with the definition of the QTPP, which should be based on the structural and functional attributes of the RP.[16] The QTPP should be considered as a development tool, which may evolve as further information on the RP becomes available.

The required definitive QTPP data are derived from extensive analytical characterization of the RP Batches incurred by the BS developer. The RP characterization data also allow a BS developer to define their initial DS and DP manufacturing process steps (e.g., from reverse engineering of identified quality attributes of the RP), as well as to establish preliminary target criteria and ranges for the BS.

Illustration of analytical characterization data on the QTPPs of some existing RP products may be found in published literature.[17] Published literature may be used to guide the analytical characterization strategy, but they shall not replace de novo characterization data of RP generated for a new BS development.

As for any biological products, the BS is defined by the quality characteristics of its DS, which is the active biological substance. This biological substance has its own heterogeneity of molecular variants, isoforms, or other product-related substances, which are defined by the recombinant expression systems as well as culturing and downstream materials and processing conditions.

The DS of a biological product including the RP and the BS also contains product-related impurities and degradants, as well as process-related impurities that cannot be entirely removed in downstream steps, such as residual host cell proteins (HCPs).

As a consequence, the DS manufacturing process of the BS should be appropriately designed (choice of expression system, design of the purification process, etc.) to achieve the QTPP and match data from RP characterization.

An initial list of QAs for the BS can be established based on the QTPP, the RP characterization studies, and the manufacturing process of the DS and DP. From this initial list of QAs, a list of CQAs where a linkage study of the QAs to potential clinical impacts of the BS on functions, PK/PD, safety/immunogenicity, and efficacy should be performed together with a risk assessment. Such risk assessment tools should consider the impact of the QAs on PK/PD, safety/immunogenicity, and efficacy. Furthermore, the degree of uncertainty of impact should be taken into consideration. If it is known that a QA will impact the clinical performance (that is, the uncertainty is low but the impact high) then that quality attribute should be prioritized and considered as CQAs, and the overall risk score should be high. In cases where the clinical relevance of a CQA is unknown (that is, the uncertainty is high) then higher risk scores should be assigned even to lower impact quality attributes. Further guidance on a variety of risk management tools (e.g., risk ranking, hazard analysis, safety assessment decision tree) to identify the CQAs for DS and DP can be found in the ICHQ9 Quality Risk Management (ICHQ9). [18]

It is acknowledged that the DS and DP manufacturing processes of the RP may undergo authorized post-approval changes through their product lifecycle. In some cases, the RP lifecycle changes may occur while a BS is under development, resulting in analytically-detectable differences in the pre-change versus post-change RP batches that are incurred for the CQE study.

A detectable shift in the range of QAs among the RP batches incurred for the CQE could impact the QTPP, making it no longer fully representative of the total population of RP batches available on the market. However, to find shifted RP batches in the market indicates they obtained successful regulatory approval of the RP post-market changes. That means the full range of pre and post change of the RP batches are (by definition) clinically qualified as safe and efficacious. Data generated from pre and post change RP batches showing a shift in attribute ranges could normally

be used to support the BS acceptance criteria ranges in the QTPP. Therefore, the BS developer should consider incurring a larger number of RP batches over a longer period of time to potentially observe greater variances, including the impact of possible shifts or drifts in the RP attributes when establishing the QTPP and the acceptable variability range for biosimilarity evaluation. It is acknowledged that the BS will also have its own Quality/CMC lifecycle. When changes to the DS or DP manufacturing processes are introduced during development – including technology transfer of the BS DS or DP manufacturing to a different site of production – a comparability exercise should be performed to compare the characteristics of the pre-change and post-change of the DS and DP according to the ICH Q5E that applies to all biological products including biosimilar after MAA approval.

If a BS developer introduced process changes before SFDA MAA approval, these changes should be supported with CQE against the RP for pre and post change batches during BS development. Where the results reveal substantial differences in CQAs between pre and post change BS batches, the impact of such differences on the CQE between the BS to the RP should be assessed.

The BS process changes made after SFDA MAA approval should follow the comparability exercise as described in ICHQ5E but does not require repeating the CQE comparing the BS to the RP.

5.1.2. Drug Substance of Biosimilar

In general, the BS must have the same primary sequence, higher order structures, posology, route of administration and MoA as the RP.

However, differences between the BS and the RP in certain quality aspects may be allowed if these differences have no impact on functions and clinical outcomes based on the result of the comparative preclinical and clinical exercises.

These include differences in the expression system i.e. the host cell line used for production (e.g., CHO K1, E. coli K12 strains), the formulation (e.g., excipients), pharmaceutical forms (e.g., powder for reconstitution or solution for injection), presentation (e.g., the number of syringes in a pack) and administration device.

The expression system should be carefully selected because differences may result in undesired consequences, such as atypical glycosylation patterns or sequence variants, or a different impurity profile, as compared to the RP. Although the BS does not need to be expressed in the same type of cell line used for the RP, it is recommended to use a similar host cell line to reduce the potential changes in CQAs relative to the RP. Careful consideration should be given to the decision to use a different expression system for a BS versus the RP.

5.1.3. Drug Product of Biosimilar

The formulation and container/closure of the BS does not need to be identical to that of the RP. However, if a different BS formulation and/or container/closure system to the RP is selected (including any material that is in contact with the medicinal product), its potential impact on the PK/PD, safety/immunogenicity, and efficacy of the BS should be appropriately justified.

Regardless of the formulation selected, the suitability of the proposed BS formulation with regard to stability, compatibility (i.e. interaction with excipients, diluents and packaging materials), integrity, activity and concentration of the DS should be demonstrated.

5.1.4. Analytical Test Methods for Biosimilar

Test methods used in the analytical control strategy for the DS and DP process and product include compendial and non-compendial procedures. Compendial test methods should be verified for use with the BS as described in the relevant pharmacopeias. Non-compendial methods should be validated for the BS in alignment with ICHQ2 Validation of Analytical Procedures (ICHQ2) as appropriate for the phase of GMP (clinical or commercial).[19] Orthogonal methods used to monitor the stability of the BS must be validated to be stability-indicating test. Test methods that are used only for characterization of the BS, or comparability exercises per ICHQ5E, or the CQE per this guideline, should be qualified to demonstrate they are scientifically sound and produce consistent and reliable results. Qualification and validation of *in vitro* bioassays should comply with appropriate ICHQ2 and USP or Ph. Eur. requirements. Publicly available international reference standards (e.g. WHO, Ph. Eur., USP) may be used in method qualification and validation, and for calibration of an in-house reference standard for potency bioassays. However, these public reference standards cannot be used as a comparator instead of, or in addition to, the RP in the CQE.

5.1.5. Specification of Biosimilar

Specifications are employed to ensure the quality and stability of the DS and the DP are monitored and controlled in a routine basis, rather than requiring a full characterization of every batch. As for any biological products, the specification of the BS should be based on manufacturing experience with the DS and DP, the characterization and stability results of the DS and DP, analytical method capabilities (based on verification or validation data) and a risk assessment of CQAs with potential impact on product and clinical performance. The specification should be described in according to the ICH Q6B Specification: Test procedures and Acceptance criteria for biotechnology/biological products (ICHQ6B). [7]

The BS specification should capture and control the CQAs that were established to support the QTPP for BS development. Reference to the analytical methods used and acceptance criteria for each test parameter of the DS and DP should be provided and justified. The verification and validation report and data for all analytical methods referenced in the specification should be documented and provided.

Although the results of the CQE may be utilized in assessing the clinically qualified ranges of product attributes, the BS manufacture should carefully consider that limits or range for a given specification are not significantly wider than the range of the variability of the RP batches over the shelf-life, unless properly justified. Although compliance with a pharmacopeia monograph specification for a given BS is not sufficient to establish biosimilarity, the BS should show the same pharmacopeias compliance level as the RP. It is important to emphasize that pharmacopeia monographs reflect minimum requirement and specification of additional tests parameters that may be required by SFDA. It is unlikely that the complete control specification of a BS will be the same as for the RP since the manufacturing processes, formulation, container/closure, analytical procedures, and testing laboratories may differ. Moreover, the RP control specification will have been refined over time based on data from numerous DS and DP batches and annual stability studies demonstrating long-term manufacturing consistency and product stability.

5.2. Considerations for Comparative Quality Exercise

An extensive CQE is performed to evaluate the QAs with more emphasis on CQAs of BS and RP to demonstrate that they are highly similar in structural and functional attributes. If differences in CQAs are confirmed (for which the absence of a clinically relevant impact will be difficult to justify), it may be challenging to claim similarity to the RP, and thus, a MAA for a new biological product may be more appropriate.

The CQE should include a wide array of sensitive and orthogonal analytical methods to compare structural attributes including primary, secondary, tertiary, and higher-order structure, plus multiple *in vitro* bioassays to compare functional attributes.

Process-related impurities such as Host cell proteins (HCPs), Host cell DNA (HC-DNA), cell culture residues and downstream processing residues may be quantitatively and/or qualitatively different between the BS and RP due to the different manufacturing processes used for their DS. The applicant should demonstrate that the desired product (including product-related substances) present in the BS is similar to that of the RP.

The CQE should include side-by-side testing of the BS and RP samples. Any qualitative and/or quantitative differences detected in CQAs will have to be appropriately justified with regard to their potential impact on functions and clinical outcomes including biological activity, PK/PD, safety/immunogenicity and efficacy.

Sensitive and orthogonal methods should be used in the CQE to determine not only similarities but also potential (minor) differences in QAs. Particular attention should be given to CQAs that might have an impact on immunogenicity (e.g., aggregates, degradants) or biological activity (e.g., higher order structure, glycosylation), or that have not been identified in the RP (e.g., HCPs).

Although biological assays may demonstrate that (minor) differences on structural attributes of a molecule have no impact on function and clinical outcomes. To ensure there are no novel potential degradation pathways between BS and RP, test samples from each should be subjected to side-by-side forced-degradation studies to qualitatively compare the degradant species formed. The risk related to any newly identified degradants in the BS should be evaluated. Differences that may confer an advantage (e.g., better long-term stability of the BS) should be explained but are unlikely to preclude biosimilarity.

For each analysis conducted in the CQE, the age and shelf life of the RP and BS samples at the time of testing should be stated, along with any other factors that could have potential effects on their quality profile (such as the in-lab storage and handling conditions of RP and BS samples). If the analyses use 'mock' DP samples of BS (see section 5.2.4.), the age of the DS of BS at the time of preparation and testing should be stated, along with the composition and concentration of the formulation components.

5.2.1. Comparative Physicochemical Properties

The physicochemical comparison of BS to RP comprises the evaluation of physicochemical attributes, which should include a determination of the composition, physical properties, primary sequence, and higher order structures, using appropriately sensitive and specific analytical methodologies.

The primary sequence of the BS should be confirmed and is expected to be the same as for the RP. Although identical primary sequence of the BS and the RP is required, low-level sequence variants may present due to transcription and translation errors, especially through amino acid misincorporation during expression for proteins. In addition, an inherent degree of sequence variants and structural heterogeneity occurs in proteins as a result of biosynthesis process.

These sequence variants and structural heterogeneity of proteins include C-terminal processing, N-terminal pyroglutamination, disulfide bond mismatch and free sulfhydryl groups and post-translation modifications (PTMs) such as glycosylation, deamidation, oxidation, isomerization, fragmentation, glycation, and aggregation. Manufacturers should thoroughly describe and quantify and carefully control any BS sequence variants or structural heterogeneities to an acceptable and consistent level.

Glycosylation is an important common PTMs for many therapeutic proteins such as monoclonal antibodies (mAbs), which involve the attachment of glycans (or carbohydrate structures) to specific sites of the protein. If present, glycosylation in the RP and BS should be thoroughly characterized; including the overall glycan profile, carbohydrate structures. site-specific glycosylation patterns as well as site occupancy. The presence of glycans not observed in the RP

may raise concerns and would require appropriate justification, with particular attention to pre-human structures (pre-human linkages, sequences, or sugars).

The BS manufacturer should carefully assess the detected differences in any sequence variants and structural heterogeneities between the RP and the BS. The BS manufacturer should also consider the assessment of potential impact of such sequence variants and structural heterogeneity on functions and clinical outcomes of the BS relative to the RP. Comparative biological activity is in general more specific and sensitive than *in vivo* studies in animals for detecting and assessing the impact of structural differences between the RP and BS.

5.2.2. Comparative Biological Activity

The biological activity describes specific ability or capacity of a product to achieve a defined biological effect and serve as surrogate for *in vivo* potency. To compare all potential biological activities of a BS to the RP, different complementary biological assays reflecting the understood MoAs for clinical activity of the DS of the RP may be necessary.

Comparative biological activity includes orthogonal and different assay formats (e.g. ligand or receptor binding assays, enzymatic assays, cell-based assays, functional assays), acknowledging their limitations. The use of relevant biological assays with suitable precision, accuracy, sensitivity, and sufficient discrimination capabilities can provide an important information of confirming that there are no significant functional differences between the RP and the BS.

Where immunochemical properties are part of the biological activity of certain RPs such as mAbs and fusion proteins, it is important to thoroughly characterize and compare the immunological properties including the specificity, affinity and binding activity relevant to the fragment crystallizable (Fc) receptors (e.g., Fcγ receptors, neonatal Fc receptor (FcRn), complement component 1q (C1q)) which should be compared using suitable analytical methods such as surface plasmon resonance and biolayer interferometry. Additionally, the ability to induce Fab- and Fc-associated effector functions (e.g., antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC), where relevant) should be compared using appropriate methodologies.

The reportable results of relevant potency biological assay(s) should be provided and expressed in units of activity calibrated against an official international or national reference standard, when available and appropriate. The publicly available official reference standard should be used to calibrate an in-house potency reference standard from the BS production process. When no official reference standard is available, or is not appropriate for the BS, the reportable results should be provided as percent relative potency as calibrated against an in-house BS product reference standard that has been appropriately established in alignment with ICHQ6B. [6]

If CQE revealed differences in biological activity, the potential impact of such differences on clinical outcomes including MoAs, PK/PD, safety/immunogenicity and efficacy should be thoroughly discussed. The correlation between biological activity (e.g., Fc-mediated effector functions, Fcγ receptors or C1q binding and structural attributes including physicochemical characteristics and PTMs such as glycosylation, should be assessed. Such assessment will facilitate the interpretation and predication of the clinical impact of minor differences between the RP and the BS.

5.2.3. Comparative Purity and Impurities

Product-related substances and product-related impurities such as variants in primary sequence or PTMs in the RP and BS should be compared using sensitive, specific, state-of-the-art technologies and orthogonal methodologies.

Product-related impurities caused by protein degradation, such as oxidation, deamidation, aggregation or fragmentation should be compared between the RP and the BS using appropriate orthogonal methods that are specific for the types of degradants.

If the CQE reveals differences in product-related substances between the RP and the BS, the impact of the differences should be investigated using functional assays and structure-activity relationship studies.

Differences in degradant profile between the RP and BS may be adjudicated in side-by-side forced degradation studies to determine if the differences are solely due to the different ages of RP and BS batches. The potential risk related to newly identified degradants in the BS that are not present

in the RP even under degrading conditions should be adequately documented and justified. Because no single analytical method can detect all potential degradation pathways of proteins, a set of orthogonal stability-indicating tests should be selected on the basis of forced degradation studies that are comprehensive (i.e., include all potential product degradation pathways, including light) and systematic (i.e., all physical and functional methods intended to monitor real-time product stability). [20]

Process-related impurities such as HCPs, HC-DNA, cell culture residues and downstream processing residues are expected to differ quantitatively and/or qualitatively due to different manufacturing processes used for the RP and the BS. Because the RP samples will be formulated DP, methods used in the CQE may not be sensitive enough to measure the level of process-related impurities present in the RP batches. The potential risk related to process-related impurities in the BS should be adequately documented and justified. However, process related impurities of the BS need to fulfill clinical requirements including safety and immunogenicity.

5.2.4. Comparative Quantity

In general, a BS is expected to have the same concentration or strength of the DS as the RP. Concentration deviations not affecting the posology might be permissible, if justified and assessed on a case-by-case basis.

The quantity of the DS of the BS should be expressed using the same measurement system as that used for the RP (that is, mass units or units of activity). A description with appropriate justification should also be included to describe how the BS quantity was calculated (including, for example, the determination of the extinction coefficient).

It is understood that the BS may not utilize the same formulation as the RP. If the formulated BS DP is not the same as the RP, such differences in formulation can significantly impact the performance of some analytical methods. For some analytical techniques, a direct or side-by-side analysis of the BS and RP may not be feasible or give limited information (e.g., due to the low concentration of DS and/or the presence of interfering excipients such as albumin). In order to minimize analytical artifacts solely due to differences in test sample preparations, the concentration of DS, the composition and concentration of all other excipients, and the solution

pH and osmolarity should be the same between the RP and BS samples used in the CQE experiments.

Where necessary, two approaches may be considered to normalize the composition and concentration of RP and BS for use in comparative analytical methods that are impacted by formulation differences. In one, the DS of the BS may be prepared as a 'mock DP' to match the DP of the RP formulation. In the other, the DS may be extracted from the RP and placed in the same matrix as the DS of the BS. In such cases, the techniques used to prepare the samples should be outlined, and their impact on the samples should be appropriately documented and discussed (e.g. comparison of active substances before and after formulation/deformulation preparation).

5.2.5. Comparative Stability and Degradation

Comparative real-time, real-condition stability studies between the RP and the BS are not required for purposes of assessing shelf life because such data are generated independently for each product's MAA. Data to support the stability of DS and DP to shipping, handling, and long-term storage should be generated according to SFDA Guidelines for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products. [21]

However, as part of the CQE, it is valuable to compare their potential degradation pathways and pattern of degradants that are formed under the same stress conditions. Such data provide further evidence that the degradation profile of the RP and the BS under the same physical and chemical challenges is comparable. Also, data from forced degradation studies may be useful in identifying variances detected in RP batches versus BS batches that are solely due to age-related changes.

Comparative accelerated degradation studies and studies under various stress conditions (e.g., high temperature, oxidation, deamidation, freeze-thaw, light exposure, and mechanical agitation) should be conducted to obtain sufficient information on product-related substances and impurities as well as degradation pathways for the RP and the BS. In order to avoid generating different degradants solely due to formulation differences, the comparative forced degradation study might need to use a DS of the BS 'mock DP' preparation to match the DP of the RP formulation, or extracted DS from RP DP to match the BS DS matrix.

5.2.6. Selection and Identification of Batches of Reference Product and the Biosimilar

The selection and number of RP and BS batches included in the CQE should be justified by the criticality of the QA(s) being analyzed, the performance capabilities of the analytical methods to generate accurate, reliable results with a high degree of confidence, the desire to assess the normal variability of the RP and BS production processes, and the approach chosen for establishing the acceptance criteria ranges between RP and BS (i.e., visual, qualitative, quantitative, statistical). Due to the inherent variability of manufacturing processes of the RP and BS, a greater number of BS and RP batches may be necessary to obtain a meaningful assessment of batch-to-batch variability.

5.2.6.1. Reference Product Batches

Every batch of the RP used in the CQE must be clearly identified (e.g. brand name, pharmaceutical form, formulation, strength, origin of the RP, batch number, expiration date, date of acquisition). Where several strengths or presentations of the RP are available, their selection should be appropriately identified and justified.

In general, multiple RP batches should be included in the CQE to encompass the inherent heterogeneity present in protein products and the expected batch-to-batch variability stemming from RP manufacturing processes. The RP batches selected for the CQE should include those that are used in comparative (head-to-head) preclinical and clinical studies.

A greater number of RP batches provides a better estimation of the true batch-to-batch variability of the RP, which will enable a more robust statistical comparison in the CQE study. Fewer RP batches may be justified in special cases such as orphan biological product where limited batches are available.

The age of RP batches should be considered as it is expected that RP batches with different ages will be included in the CQE. The selected RP batches should span the range of RP shelf life as indicated by the expiration dates on each batch. The age of the different batches of RP (relative to the expiry dates) should also be considered when establishing the target quality profile.

The selected RP batches should also be sourced over an extended period of time to increase the potential of encompassing DP batches of RP derived from different batches and different ages of bulk DS. Incurring RP batches over a longer time period enhances the possibility of detecting shifts or drifts in RP attributes due to its approved post-market lifecycle changes.

The incurred RP batches should be carefully handled, transported and stored under recommended storage conditions. The date of the analytical testing as well as the product expiration date should be documented in the CQE. Each Batch of RP should be used within the approved shelf life dated by the date of expiry.

Although a random sampling of the RP batches is desirable, it may not be possible in practice due to availability issues. However, sampling of the RP batches should be carefully managed to capture the inherent variability of the RP batches.

In general, expired RP batches should not be included in the CQE because batches analyzed beyond their expiration date could lead to results outside the range that would normally be observed in unexpired batches, which may result in overestimated RP variability. Any exception to this would have to be fully substantiated with experimental data. For example, using RP batches past expiry may be acceptable if samples are stored under long term conditions (e.g., frozen at -80°C) and sponsors submit data and information demonstrating that frozen storage (including expected freeze/thaw cycles) does not impact the quality of the RP batches.

If the DS has been extracted from the RP batches to conduct any of the CQE tests, the extraction procedure should be described in detail, and data should be provided to demonstrate that the procedure itself does not alter relevant QAs of the RP. Reverse-engineering of the RP (extraction of DS) would include consideration of alteration or loss of the desired products and impurities and relevant product related substances, and it should include appropriate controls to ensure that relevant characteristics of the protein are not significantly altered by the extraction procedure.

5.2.6.2. Biosimilar Batches

The extent of BS process development design (as described in guidelines ICHQ8 and ICHQ11) and process understanding may be used in support of the number of proposed BS batches proposed for inclusion in the CQE.

In general, multiple independent BS batches should be included in the CQE to encompass the inherent batch-to-batch variability of the BS manufacturing processes. The BS batches selected for the CQE should include those that are used in comparative (head-to-head) preclinical and clinical studies. A single DP batch from a single DS batch would be considered independent BS batch, whereas different DP batch produced from the same DS batch would not be considered as independent BS batch.

Detailed manufacturing information of these BS batches should be clearly indicated in the CQE study (manufacturing date and site, age at time of testing, scale and use of batch e.g. development, clinical, commercial, stability, in-house reference standard; etc.).

The BS batches included in the CQE study should be manufactured using the intended commercial DS manufacturing process. Small or pilot scale batches of DS may be included only if comparability of small/pilot scale and commercial batches has been adequately demonstrated using the analytical principles of ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Processes (ICHQ5E). [9]

If batches of DS of the BS are 'mock' formulated to match the concentration and composition of the RP to minimize formulation artifacts in any of the CQE tests, the formulation procedure should be described in detail, and data should be provided to demonstrate that the mock formulation does not alter relevant CQAs as compared to the intended BS formulation.

5.2.7. Use of Official Biological Product Reference Standards

Publicly available official reference standards of biologicals established by reference standard organization such as WHO, USP or Ph. Eur. Pharmacopeia monographs cannot be used as the RP for demonstration of biosimilarity. Furthermore, official reference standards cannot be used as RP in a CQE because they are not in the same formulation or presentation as for clinical use of an RP, they cannot reflect what patients have been given in clinical practice and have no clinical safety

and efficacy records. [22] Official reference standards are derived from bulk DS batches that are specifically formulated, vialed, and stored to maintain a calibrated potency value that has been assigned through an interlaboratory study. Excipients necessary to optimize the retention of biological activities (such as albumin) may interfere with other analytical methods used in the CQE.

The official reference standard is a valuable material for use in the development of a BS, bioassay method development, qualifying/validating of bioassays for their intended use, for calibrating in-house BS reference standards for potency bioassays, and for monitoring bioassay performance throughout the life-cycle of a BS.

In the biopharmaceutical field, official reference standards are used for monitoring the potency of individual/diverse RPs and BSs, and harmonizing RP and BS dosing for patients globally. They are also used for confirmatory testing of falsified medicines, and as independent standards for aligning potency values between RP and BS batches (horizontally) and over time across multiple batches of an individual RP or BS (longitudinally) to support post-approval surveillance activities and to assess any potential divergences following RP or BS post-approval manufacturing changes.[23]

5.2.8. Analytical Method consideration

Extensive analytical characterization studies should be applied to both the RP and the BS using state-of-the-art (bio)chemical, (bio)physical, (micro)biological analytical methods and techniques to demonstrate with a high level of assurance that the quality of the BS is comparable to the RP.

It is the responsibility of the MAA to demonstrate that the selected methods used in the CQE would be able to detect slight differences in all aspects pertinent to the evaluation of quality (i.e., ability to detect relevant variants with high sensitivity).

Characterization methods used in the CQE should be appropriately qualified to demonstrate they are scientifically sound, appropriately sensitive, and specific, and can produce consistent and reliable results for the purpose of comparing the BS to the RP. Qualification of *in vitro* bioassays

should include the appropriate ICHQ2 and USP or Ph. Eur. parameters. Calibration of potency bioassays should include official reference standards, where applicable for the BS.

The measurement limitations of each analytical method should be considered when assessing the comparability between the RP and the BS. For example, it is important to note that many analytical test methods used with biological products (especially *in vitro* bioassays) may have relatively high variability that might preclude the detection of minor differences between the RP and the BS. This variability may necessitate high enough number of replicates and runs of each test method to provide sufficient confidence in the accuracy of results for a reliable evaluation of analytical biosimilarity of the RP and BS. Therefore, the replication scheme for some methods used in the CQE may be more rigorous than when the same test methods are used in routine BS specification testing.

Data obtained from the CQE should be provided, including physicochemical properties (e.g., primary, and higher order structures, post-translation modifications), purity and impurities, product-related substances/variants, *in vitro* biological activities, and immunochemical properties (if the product is a mAb or fusion protein). The CQE results should include data and information from all RP and BS batches intended in the study protocol. If an RP or BS batch is specifically selected to be included or excluded from certain analytical studies, a justification should be provided with regard to potential impact on safety and efficacy.

The CQE data should be presented clearly and comprehensively, sufficiently to allow independent interpretation of results and substantiation of the discussion of the findings. Where (minor) differences are detected between the RP and the BS in some QAs, explanation and justification should be provided.

Data presentation in the CQE depends on the nature of each analytical method.

- Methods that produce qualitative results should present the data in the format most suitable for direct comparative evaluation.

- Methods that generate quantitative numerical results should present the data in tabular form, with indication of the replication scheme used to generate the reported values.

- Methods that generate peaks, bands, curves (e.g., gels, electropherograms, chromatograms, spectral traces, binding kinetics, dose-response curves) should present representative high-quality images of the RP and BS raw data in a manner to allow direct visual assessment.

- If raw image data is further subject to quantitative analysis (e.g. integration, parallelism, rate determination), representation of the analysis parameters should be included.

5.2.9. Statistical Approaches

Prior to initiating the CQE study, it is recommended that the QAs of the RP are identified and ranked according to their criticality and impact on the clinical performance of the product as described in section 5.1.1.

The result of the risk ranking of QAs could then be used to guide the statistical approaches to be used in the CQE. A descriptive statistical approach to establish biosimilarity ranges of CQAs could be used, if appropriately justified. The relevance of the biosimilarity ranges should be discussed, considering the number of RP batches tested, the QAs investigated, the age of the RP batches at the time of testing and the demonstrated inherent variability of each qualified analytical test method. The biosimilarity ranges should be based primarily on the measured CQA ranges of the RP and should not be wider than the range of variability of the representative RP batches, unless it can be determined which differences would be acceptable (for example, less impurities is usually acceptable). Wide biosimilarity ranges based on inappropriate use of statistical approach should not be used. It should be noted that biosimilarity ranges used for the CQE should be addressed separately from specification acceptance criteria.

The most frequently applied overall biosimilarity criteria requires that certain percentages of the BS batches (usually between 90% and 100%) fall within predefined biosimilarity range based on the analysis of the RP batches.

Various statistical approaches can be used to establish the CQE acceptance criteria.[24,25] Commonly used statistical approaches include, the min-max ranges, x-sigma range, tolerance intervals and equivalence testing of means. However, each statistical approach has specific strengths and limitations that should be acknowledged and considered during CQE evaluation. The

applicant should support the selection of such statistical approach with proper discussion and justification. The selection of the statistical approach should be driven by the specific nature of the CQAs and the performance characteristics and suitability of the analytical methods used in the CQE

- The x-sigma intervals (mean ± X SD) is the most common and practical approach. The multiplier X should be scientifically justified and could be linked to the criticality of the QA tested, with a smaller multiplier for high criticality QAs. However, the inherent variability of each qualified analytical method should also be considered; the acceptance criteria for comparing BS to RP with each analytical method should not be tighter than the precision and accuracy of repeated measurements of either product in the same method.

- The min-max range of the RP batches is the most conservative approach, which could be viewed as clinically qualified because they reflect the RP batches being on the market and used by patients in clinical practice. Nevertheless, the min-max range maybe associated with high risk of a false-negative conclusion, meaning that a high risk of concluding the RP and BS are not similar, even though the overlapping distribution of the underlying analytical data for the RP and BS support a conclusion of similarity.

- The tolerance intervals (TI) would require a high number of the RP batches to establish a meaningful range because a TI is a statistical interval within which, with some confidence level, a specified sampled proportion (i.e., the selected RP batches) of a population (all RP batches) falls. If limited number of the RP batches are included in the CQE, the TI can result in a wider estimation than the actual min-max ranges. This limitation could increase the risk of a false-positive conclusion of the biosimilarity, meaning a high risk of concluding the BS and RP are similar even though the underlying analytical data distribution do not overlap sufficiently enough to support the conclusion of biosimilarity of the RP and BS.

- The equivalence testing of the means (EQT) require a higher number of batches of both RP and BS, because larger sample sizes lead to greater precision of data for each product, which provides greater confidence in comparing the mean differences. However, if there

is a lack of alignment of the EQT with the equivalence hypothesis (i.e., test population in the reference population), this leads to an undesired increase of the false acceptance rate with increasing sample size. This means when more batches of RP and BS are used in the CQE to generate more precise mean values for each, the differences between the means become more pronounced and may fail statistical equivalency tests. Conversely, using fewer Batches of RP and BS increase the imprecision of the means, making more likely that they will pass statistical equivalency testing but provide lower confidence in the accuracy of the results.

In order to mitigate the risks inherent in employing statistical approaches on limited samples (false-positive and false-negative conclusions), a comprehensive analytical control strategy must be established for the BS to ensure consistent manufacturing of its DS and DP.

6. Glossary

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

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

Biosimilar: a biopharmaceutical product highly similar to an already approved RP 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 Quality Exercise: The analytical study conducted with the biosimilar product and the reference medicinal product to compare their structural and functional quality attributes.

Contaminants: Any adventitiously introduced materials (e.g., chemical, biochemical, or microbial species) not intended to be part of the manufacturing process of the drug substance or drug product.

Control strategy: A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

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.

Degradation Products: Molecular variants resulting from changes in the desired product or product-related substances brought about over time and/or by the action of, e.g., light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Such changes may occur as a result of manufacture and/or storage (e.g., deamidation, oxidation, aggregation, proteolysis).

Desired product: The molecular entity which is expected from the DNA sequence and anticipated post-translational modification (including glycoforms), resulting from the intended downstream purification to produce an active biological molecule. It may be referred to as the "active substance" or "active pharmaceutical ingredient" in other documents.

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.

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 medicinal product. The excipients need to be declared in the labelling and package leaflet of the medicine to ensure its safe use.

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.

Finished Dosage Form: The drug product filled into the container/closure system intended for clinical use, such as stoppered vial or prefilled syringe.

Generic medicine: a small molecule medicine that is structurally identical to an originator product (comparator) for which the patent and/or data protection period has expired.

Head-to-head comparison: direct comparison of the properties of a biosimilar with its corresponding **reference product**.

Immunochemical properties: The biological activity of a **monoclonal antibody (MAb) product** to bind to a target protein or cluster of proteins as its mechanism of action. Immunochemical properties of a MAb product are desired product attributes and differ from immunogenicity responses from biopharmaceutical products.

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

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.

Marketing authorization holder: any person or legal entity that has received a marketing authorization or license to manufacture and/or distribute a medicine. It also refers to a person or legal entity allowed to apply for a change to the marketing authorization or license. Under the same license, the marketing authorization holder could have several manufacturing sites registered. Therefore, several manufacturers could be involved.

Official Reference Standard: a measurement standard such as an international, pharmacopoeial or national standard – it should be noted that reference standards are distinct from reference products and serve a different function.

Originator product: a medicine that has been licensed by an NRA 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.

Posology: dosage for each indication and each method/route of administration. Information includes dose recommendation (for example, in mg, mg/kg or mg/m2), frequency of dosing (for example, once or twice daily, or every 6 hours) and treatment duration.

Potency: The measure of biological activity using a suitably quantitative biological assay (also called potency assay or bioassay), based on the attribute of the product which is linked to the relevant biological properties for product mechanism of action.

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.

Product-Related Substances: Molecular variants of the desired biological product (e.g., isoforms) which 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 (QRM): A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

Quality Target Product Profile (QTPP): A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

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 an RP.

Test Method Qualification: A protocol-driven experimental study to establish the performance capabilities of an analytical method for ICHQ2 parameters (such as specificity, linearity, range, LOD/LOQ, accuracy, precision, and intermediate precision) as applicable to the intended use of the method. Methods used only for characterization, comparability, or similarity studies should be qualified to demonstrate they are scientifically sound for.

Test Method Validation: A protocol-driven experimental study with pre-determined acceptance criteria to confirm the performance capabilities of an analytical method for ICHQ2 parameters (such as specificity, linearity, range, LOD/LOQ, accuracy, precision, intermediate precision, and robustness) as applicable to the intended use of the method. Methods used for release and stability testing should be validated with a phase-appropriate degree of rigor to assure the accuracy and reliability of reportable results for product specifications.

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