Arab Republic of Egypt
Egyptian Drug Authority
CA of Biological and Innovative products and clinical studies.
GA of Biological products
Registration Directorate

جمهورية مصر العربية
هيئة الدواء المصرية
الادارة المركزية للمستحضرات الحيوية والمبتكرة والدراسات الاكلينيكية
الإدارة العامة للمستحضرات الحيوية
إدارة التسجيل

GUIDELINE FOR REGISTRATION OF BIOSIMILAR PRODUCTS IN EGYPT

March 2020

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I. Introduction

Regulations for registration of biological products have been implemented in Egypt since 2009 through the Minister decree 297/2009 adopting guidelines for submission of registration dossier based on full data (quality, preclinical and clinical).

A Guideline for Registration of Biosimilar Products in Egypt was issued in 2014 where it has been published and implemented since then. This Guideline is a replacement of the published Guideline for Registration of Biosimilar Products in Egypt according to the updated international guidelines and as per registeration requirements for locally and imported biosimilar products where an applicant for registration of a biosimilar product should follow and fulfill.

II. Background

The difference between the term generics used for description of the copies of a reference pharmaceutical product and the term biosimilars used to describe the similar versions of a reference biological product should be clearly understood. The term generic is used to desrcibe medicinal product with a chemical drug substance of small molecule that is structurally and therapeutically equivalent to that of an originator product.

The demonstration of bioequivalence of the generic medicine with a reference pharmaceutical product is usually appropriate and sufficient to prove therapeutic equivalence between the generic medicine and the reference pharmaceutical product.

However, the guidelines for development, evaluation and registration of generic medicines is not suitable for biological products because biological products consist of relatively large, and complex proteins that:

1- Are Difficult to characterize/analyze all the quality attributes contributing to the Safety and Efficacy profile

2- Are highly dependent on manufacturing process that affects Product quality, safety and tendency to induce an unwanted immune response as well as efficacy profile.

Therefore two approaches for registration of a Similar version of a Biological Medicinal Product can be applied:

1- ***Stand-alone approach***: the manufacturer perform complete product development program (quality, pre-clincal and clincal studies) (out the scope of this guideline).

2- ***Biosimilar approach***: the manufacturer perform complete product CMC development process in addition to complete comparability quality exercise, and reduced preclinical and clinical comparability studies in order to demonstrate biosimilarity of the proposed biological medicinal product to a reference one.

III. Scope

These guidelines apply to well characterized Biological Medicinal Products developed by means of biotechnology (including recombinant DNA technology). Vaccines and plasma derived products and their recombinant analogues are excludeded from the scope of these guidelines.

IV. Definitions

Biological products: Medicinal products made of substances extracted from or produced by living sources whether they are genetically modified living organisms or liquids and tissues extracted from various human or animal sources.

Biosmilar: A similar biological medicinal product having the same active substance, dosage form, concentration and route of administration of a reference biological product and has proven through a comparability program that its quality, safety and efficacy are highly similar to a reference product when prescribed in a claimed indication.

Generic: A Copy of a medicinal product with chemical, small molecule drug substance(s) that is/are structurally and therapeutically equivalent to that/those of an originator pharmaceutical product.

Reference Biological product: A Product developed and registered on basis of complete dossier with full qualtity, preclinical and clinical data and used by the manufacturer for comparability studies versus a product supposed to be a biosimilar.

Comparability exercise: Head-to-head comparison of a biological product with a licensed reference biological product with the goal to establish similarity in quality, safety, and efficacy. Products should be compared in the same study using the same procedures.

Pilot Scale batches: The production of the drug substance or drug product by a procedure fully representative of and simulating that to be applied at manufacturing scale. The methods of cell expansion, harvest, and product purification should be identical except for the scale of production.

Manufacturing scale batches: Batches of a finished product manufactured at production scale by using production equipment in a production facility as specified in the dossier

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

Reference Countries: An updatable list of countries approved by the Technical committee for drug control.

V. Registration of a biosimilar product

Two approaches are applied for registration of biosimilar products:

I. For Imported products:

The Finished Products that Must be registered & marketed in their Country of Origin & they iclude the following 2 categories :

a) The finished product is manufactured,primary and secondary packaged in the country of origin.

a.1 The finished product is completely manufactured & imported from one of the reference countries.

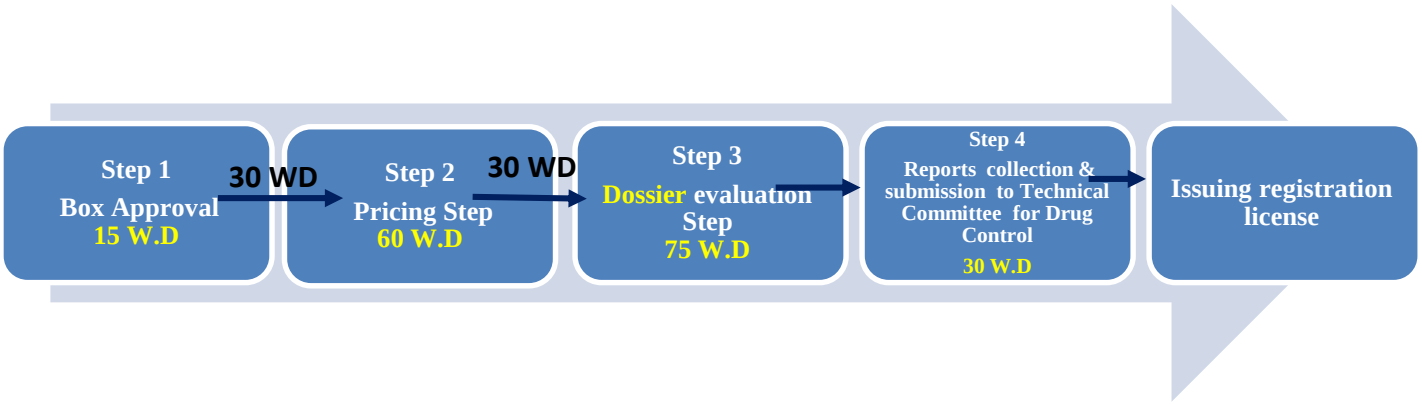
a.2 The finished product is completely manufactured & imported from one of the non-reference counteries.

b) The finished product is imported as naked container (in the final primary packaging) to undergo secondary packaging by a local manufacturer.

b.1 The nacked container is imported from one of the reference counteries to be labelled & secondary packaged locally.

b.2 The nacked container is imported from one of the non-reference counteries.

• ***The steps of registration in case of a.1 & b.1 (Importation from Refence counteries) are as follows:***



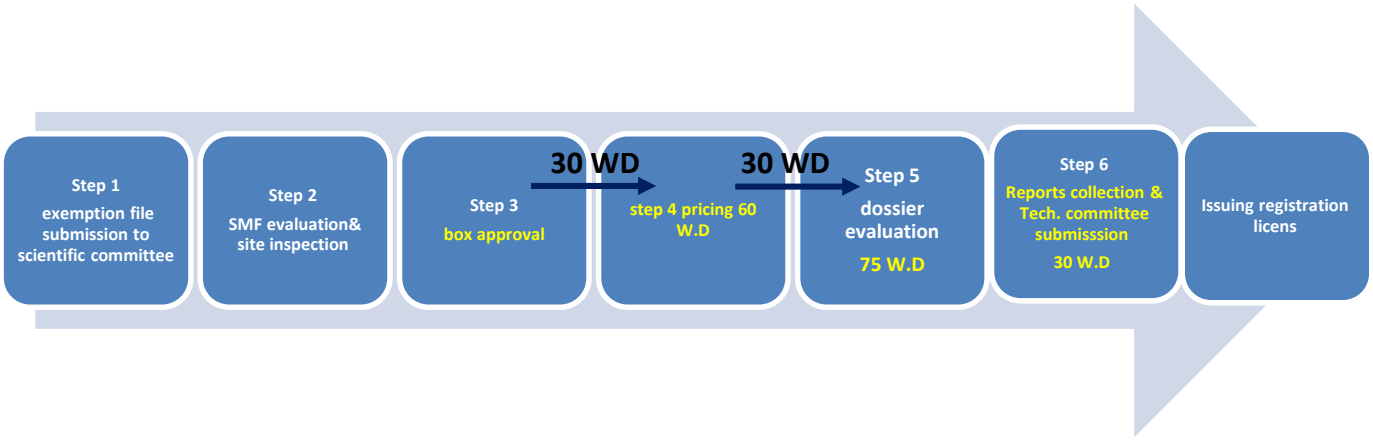
-**W.D:** Working Days.

- **Step 1:** The applicant submits an inquiry for box approval, A box approval or disapproval will be issued within 15 W.D for products submitted for Registration through Ministerial Decree 297/2009 or within the specified working days as mentioned in the Ministerial Decree 820/2016.

- **Step 2 :** The applicant should submit the *Pricing Dossier* within 30 W.D from the date of issuing the box approval . The *Pricing Certificate* is released within 60 W.D.
- **Step 3 :** The applicant is allowed to submit the *MA File* to CAPA:
  - During 30 W.D from the date of pricing certificate issuance, for products submitted for registration through Ministerial Decree 297/2009, MA file will be evaluated by all evaluation departments and analysis for registration will be performed within 75 W.D.
  - Just after submission of Pricing File, for products submitted for registration through Ministerial Decree 820/2016, MA will be evaluated within the specified W.D as mentioned in Ministerial Decree 820/2016.

- **Step 4:** Reports collection & submission to Technical Committee for Drug Control to issue the Registration License within 30 W.D.

- ***The steps of registration in case of a.2 & b.2 are as follows :***



- **Step 1:** The applicant submits an application inquiry for box approval, if the box is opened the applicant will be asked to submit exemption request to the Scientific Committee to be evaluated by the committee, then the committee decision will be submitted to the Technical Committee.
- **Step 2:** After the approval of the Technical Committee, the applicant should submit the *Site Master File* for evaluation by Biological Inspection Department; in case of approval of the submitted SMF the inspection department shall inspect the site for compliance with GMP.
- **Step 3:** Issue box approval for the submitted product after the Technical Committee approval on the *Inspection Report* of the site.
- **Step 4*:*** The applicant submits the *Pricing Dossier* within 30 W.D of receiving box approval. Pricing license is issued within 60 W.D
- **Step 5*:*** The applicant submits the *Registration Dossier* within 30 W.D of receiving pricing license, and evaluation of the submitted file and analysis for registration will be within 75 W.D in case of registration through Ministerial Decree 297/2009 or within the W.D mentioned in the Ministerial Decree 820/2016 in case of registration through this Ministerial Decree.
- **Step 6:** Reports collection & submission to Technical Committee for Drug Control to issue the Registration License within 30 W.D.

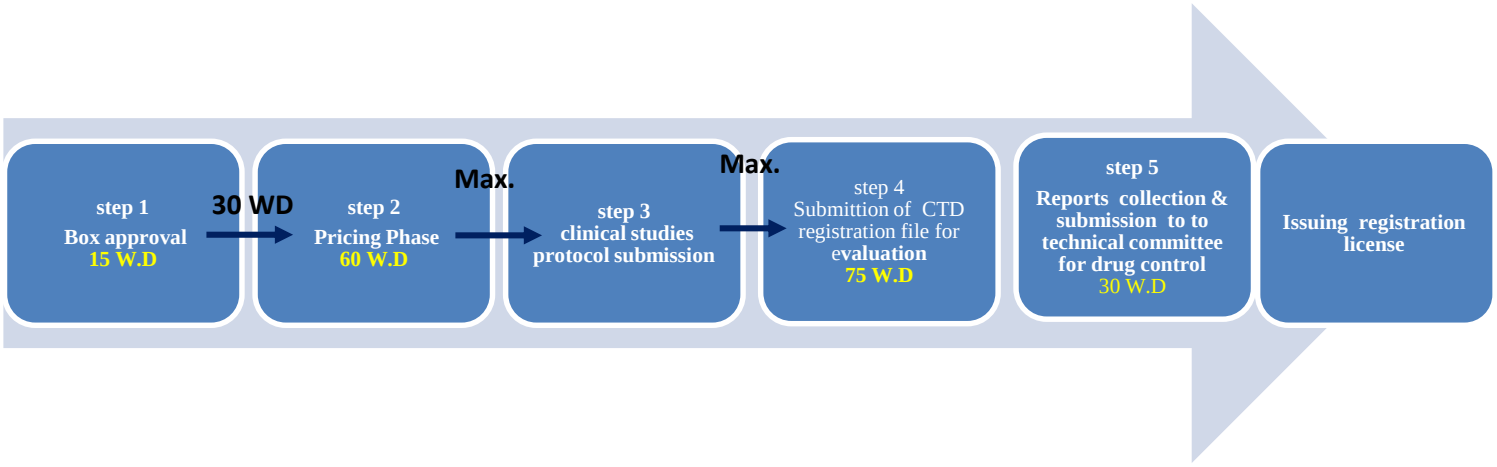
II. For locally manufactured products:

They are finished products manufactured in factories licensed in Egypt & include the following categories:

a) Manufacturing finished product starting from developing drug substance to the final finished product in local factory/factories.
b) Manufacturing finished product starting from imported drug substance.
c) Manufacturing finished product starting from imported concentrated finished product bulk for further formulation in local manufacturer.
d) Filling for Imported finished product bulk (Ready for filling bulk).

**The Regulatory Authority will conduct inspection for the manufacturing sites for both imported drug substance & finished product bulk by inspection department.*

- ***The steps of registration of categories (a) , (b) & (c) are as follows :***



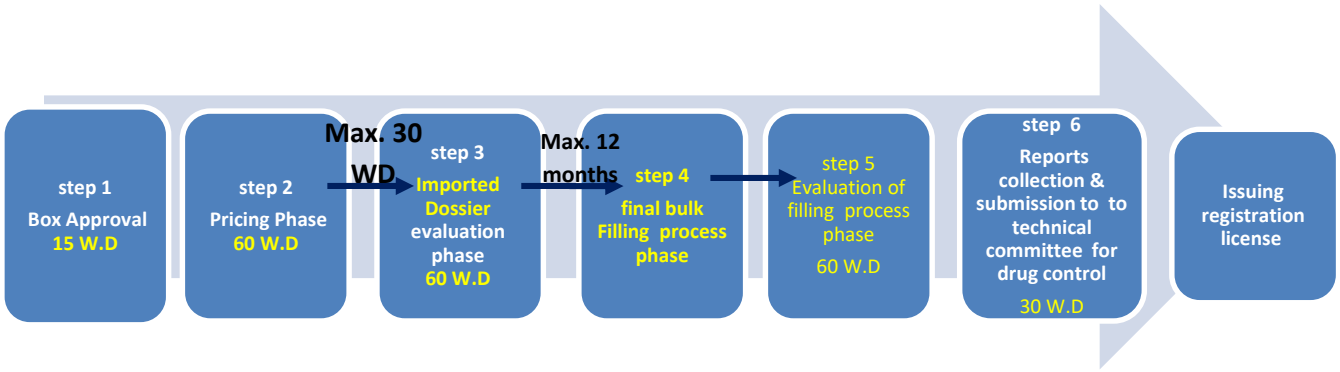
- ***step1*:** The applicant submits an application inquiry for box approval, A box approval or disapproval is issued within 15 W.D in case of registration through Ministerial Decree 297/2009 if the box is opened, the following phases/steps have to be completed
- ***Step 2*:** The applicant submits the pricing dossier within 30 W.D of receiving box approval
- Pricing license is issued within 60 W.D with 2 years validity period (can be extended by a justified request from the applicant).
  - During this 2 years:
    - The applicant is allowed to purchase (in case of imported active substance) or produce (in case of locally manufactured active substance) specified amount of active substance required for manufacturing specified batch sizes for

development *(Optional: the applicant in this stage can request for assessment of the active substance master file & the site master file)*

- The applicant has to develop the biosimilar product, perform the quality and *Preclinical Comparability Studies* along with the preparation of *Clinical Studies protocol*. At any stage, the results of quality and preclinical studies as well as the clinical studies protocol could be submitted for scientific advice.

- ***Step 3*:** the applicant submit the clinical studies protocol for evaluation, An approval to conduct clinical studies will be issued with 4 years validity period (can be extended by a justified request from the applicant).
- After completion of the clinical studies, the applicant completes the *Registration Dossier* to be submitted as CTD format for validation and assessment.
- ***Step 4*:** An assessment of registration dossier and analysis for registration are performed during this phase and the final assessment report is issued within 75 W.D
- ***Step 5*:** Reports collection for submission to Technical committee for drug control within 30 W.D.

- ***For case d) the following registration workflow should be followed:***



N.B: All requirements for registration of imported product should be fulfilled for steps 1,2,3.

- Step 4: For (Final bulk filling process) should follow *ICH Q5E - Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing process*; a guideline for changing filling site of finished product (technology transfer guidelines) is followed.

- Step 5 : Evaluation of quality part concerning filling process including stability study after filling ,and analysis for registration will be preformed.

Where a determination of comparability can be based on a combination of analytical testing, biological assays, and, in some cases, nonclinical and clinical data. If a manufacturer can provide assurance of comparability through analytical studies alone, nonclinical or clinical studies with the post-change product are not warranted. However,where the relationship between specific quality attributes and safety and efficacy has not been established, and differences between quality attributes of the pre- and post-change product are observed, it is appropriate to include a combination of quality, nonclinical, and/or clinical studies in the comparability exercise.

VI. Principles for Development of Biosimilar products

Development of biosimilar product together with proving biosimilarity relys on the manufacturer of the drug product, whether the drug substance manufacturer is the same entity of the drug product manufacturer or a contract manufacturer. If the manufacturer of the drug substance differs from that of the drug product, it will be the applicant's responsibility to provide the regulatory authority with the active substance full data within module either by his own submission or directly by the manufacturer of the active substance.

1- Rational for choice of the Reference Biological product should be provided in the submission:

- A **single reference** medicinal product should be used as the comparator throughout the comparability program for quality, safety and efficacy studies during the development of a biosimilar in order to allow the generation of coherent data and conclusions.
- The reference medicinal product used in the biosimilar comparability exercise at the quality level must be clearly identified (e.g. brand name, pharmaceutical form, formulation, strength, origin of the reference medicinal product, number of batches, lot number, age of batches, use). Where several strengths or presentations are available, their selection should be appropriately justified
- In case of using other version of the reference medicinal product (i.e. licensed by other competent authority than that of the country of origin), it will be the applicant's responsibility to demonstrate that

the comparator (i.e. the other version of the reference medicinal product) is representative of the reference medicinal product.

- Publicly available reference standards (e.g. Ph. Eur.) cannot be used as the reference medicinal product for demonstration of biosimilarity. However, the use of these standards plays an important role in method qualification and standardization.

➢ ***The Reference Biological Product should fulfill the following criteria:***

- Drug substance of the Reference biological product and that of the biosimilar product must be similar.
- Authorized on basis of complete dossier (full Quality, Preclinical and Clinical data). Therefore an Approved biosimilar cannot be considered as a Reference product.
- In case of using a reference medicine that has not been registered in Egypt, the reference medicine must be approved and marketed in a reference country (for example, EU or US) before request submission.

(N.B: it's recommended for the applicant during development process to monitor all the data regarding the safety and efficacy of the refrence product)

(N.B: In case the reference product is not licensed in Egypt the company shall provide samples from the reference product together with the internal reference standard and the samples of the proposed biosimilar product for analysis)

For the Finished product both Biosimilar and Reference medicinal product must have the same posology and route of administration. Some differences may be allowed if they have no effect on safety and efficacy - for example differences in the formulation of the medicine (e.g. excipients), presentation (e.g. powder to be reconstituted versus solution ready for injection) and administration device (e.g. type of delivery pen). Deviations from the reference product as regard strength, pharmaceutical form, formulation, excipients or presentation require justification. If needed additional data should be provided. Any differences should not compromise safety.

- To ensure that the full range of product variability is accurately captured, sponsors should acquire multiple reference product lots throughout the development program of a proposed biosimilar in sufficient quantity to conduct multiple physiochemical and functional assays.
- Considering the inherent heterogeneity present in protein products and the expected lot-to-lot variability stemming from manufacturing processes, it is recommended that a sponsor include multiple reference product lots (acquired over a time frame that spans expiration dates of several years (i.e. shelf life), in the analytical assessment to ensure that specification limits capture not only the variability of the reference product manufacturing process but also variability due to product instability during storage.

1- Expression System:

Therapeutic protein products can be produced in microbial cells (prokaryotic or eukaryotic), cell lines (e.g., mammalian, avian, insect, plant), or tissues derived from animals or plants. It is expected that the expression construct for a proposed product will encode the same primary amino acid sequence as its reference product. However, minor modifications, such as N- or C terminal truncations (e.g., the heterogeneity of C-terminal lysine of a monoclonal antibody) that are not expected to change the product performance, may be justified and should be explained by the sponsor .

Possible differences between the chosen expression system (i.e., host cell and the expression construct) of the proposed product and that of the reference product should be carefully considered because the type of expression system will affect the types of process- and product-related substances, impurities, and contaminants (including potential adventitious agents) that may be present in the protein product. For example, the expression system can have a significant effect on the types and extent of translational and posttranslational modifications that are imparted to the proposed product, which may introduce additional uncertainty into the demonstration that the proposed product is biosimilar to the reference product. More extensive comparability exercise should be employed to assure quality, efficacy and safety of the biosimilar product, if the manufacturer used host cell type different from that of the reference biological .

Minimizing differences between the proposed product and reference product expression systems to the extent possible can enhance the likelihood of producing a biosimilar protein product. Use of different expression systems will be evaluated on a case-by-case basis.

2- Manufacturing Process

A comprehensive understanding of all steps in the manufacturing process for the proposed product should be established during product development. Information gained during process development including characterization tests, process controls and specifications must be specific for the proposed product and manufacturing process.

The development and documentation for biosimilar should cover two distinct aspects:

i) *Molecular characteristics* and *Quality Attributes* (QA) of the target product profile should be comparable to the reference medicinal product;

-The *Quality Target Product Profile* (QTPP) of a biosimilar should be based on data collected on the chosen reference medicinal product, including publicly available information and data obtained from extensive characterization of the reference medicinal product. Since The biosimilar medicinal product is defined by the molecular composition of the active drug substance resulting from its manufacturing process, which may introduce its own molecular variants, isoforms or other product-related substances as well as process-related impurities. As a consequence, the manufacturing process should be appropriately designed to achieve the QTP.

ii) *Performance and Consistency of the Manufacturing Process* of the biosimilar on its own.

-The use of enhanced approaches to pharmaceutical development, along with quality risk management, effective quality systems and implementing Good Manufacturing Practices, will facilitate the consistent manufacturing of a high-quality product.

- A biosimilar is manufactured and controlled according to its own development, taking into account state-of–the-art information on manufacturing processes and consequences on product characteristics.

- The following guidelines should be considered in the development process:

a. *ICH Q5D Derivation and characterisation of cell substrates used for production biotechnological/biological products.*
b. *ICH Q5B Quality of biotechnological products: analysis of the expression construct in cells used for production of r-dna derived protein products.*
c. *ICH Q5A (R1)Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin shall be followed for cell line qualification .*
d. *ICH Q8(R2) Pharmaceutical Development*
e. *ICH Q9 Quality Risk Management*
f. *ICH Q10 Pharmaceutical Quality System*
g. *ICH Q11: Development and manufacture of drug substances–chemical and biotechnological/biological entities.*
h. *ICH Q5C Quality of biotechnological products:stability testing of biotechnological/ iological products.*
i. *ICH Q6B Specifications: test procedures and acceptance criteria for biotechnological/biological products*

VII. Comparability Key elements

- A stepwise approach is normally recommended throughout the biosimilar product development program, starting with a comprehensive physicochemical and biological characterization. The extent and nature of the non-clinical in vivo studies and clinical studies to be performed depend on the level of evidence obtained in the previous step(s) including the robustness of the physicochemical, biological and non-clinical in vitro data.

- Generally, the aim of clinical data is to address slight differences shown at previous steps and to confirm comparable clinical performance of the biosimilar and the reference product. Clinical data cannot be used to justify substantial differences in quality attributes.

- An extensive head to head comparability exercise will be required to demonstrate that the biosimilar has a highly similar quality profile when compared to the reference medicinal product. This should include comprehensive analyses of the proposed biosimilar and reference medicinal product using sensitive and orthogonal methods to determine not only similarities but also potential differences in quality attributes. These analyses should include *side-by-side comparative studies* unless otherwise justified. *Any differences detected in the quality attributes will have to be appropriately justified with regard to their potential impact on safety and efficacy.*

- Collecting data from publically available information and data from extensive analytical characterization for different batches of the reference product, will enable the applicant to:
- Achieve the quality target product profile (QTPP) of the proposed biosimilar.
- Detect batch to batch variation within batches of the same reference product.
- Specify the acceptance criteria for biosimilarity with justification.
- The aim of the biosimilar comparability exercise is to demonstrate that the biosimilar product and the reference medicinal product chosen by the applicant are similar at the level of the finished medicinal product. It is not expected that all quality attributes of the biosimilar product will be identical to the reference medicinal product. However, where qualitative and/or quantitative differences are detected, such differences should be justified and, where relevant, demonstrated to have no impact on the clinical performance of the product (this may include additional non-clinical and/or clinical data)
- Particular attention should be given to quality attributes that might have an impact on immunogenicity or potency, or that have not been identified in the reference medicinal product.
- For proving similarity with the reference product during comparability exercise, data from suitable number of batches, of the proposed biosimilar product at time of submission should be provided, as well as complete CMC data in CTD format according

to ICH guidelines, preclinical and clinical comparative studies with the same reference product used in the quality comparability exercise should be submitted.

- Differences in quality pattern between the biosimilar and the reference product of unknown clinical relevance, particularly regarding safety should be addressed in additional studies pre-marketing.
- Differences in quality pattern between the biosimilar and the reference product that is known to have potential impact on clinical activity will influence the judgment whether to consider the product as a biosimilar or not. (For example, if differences are found in glycosylation patterns that alter the bio-distribution of the product and thereby change the dosing scheme, then this product cannot be considered a biosimilar product.).
- It is the responsibility of the applicant to demonstrate that the selected methods used in the comparability exercise would be able to detect slight differences in all aspects pertinent to the evaluation of quality. Methods used in the characterization studies form an integral part of the quality data package and should be appropriately qualified for the purpose of comparability (e.g. ability to detect relevant variants with high sensitivity).
- For some analytical techniques, a direct or side-by-side analysis of the biosimilar and reference medicinal product may not be feasible or give limited information (e.g. due to the low concentration of active substance and/or the presence of interfering excipients such as albumin). Thus samples could be prepared from the finished product (e.g. extraction, concentration, and/or other suitable techniques). 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/de-formulation preparation).
- Quantitative ranges should be established for the biosimilar comparability exercise, where possible. These ranges should be based primarily on the measured quality attribute ranges of the reference medicinal product and should not be wider than the range of variability of the representative reference medicinal product batches, unless otherwise

justified. The relevance of the ranges should be discussed, taking into account the number of reference medicinal product lots tested, the quality attribute investigated, the age of the batches at the time of testing and the test method used.

- It should be noted that acceptable ranges used for the biosimilar comparability exercise versus the reference medicinal product should be handled separately from release specifications.
- The Age/Shelf Life of the reference medicinal product at the time of testing should be mentioned, and its potential effect on the quality profile should be discussed where appropriate.
- Comparison of relevant Quality Attributes, tested at selected time points and storage conditions (for example, accelerated or stress conditions), could be used to further support the Similarity of the Degradation Pathways of the reference medicinal product and of the biosimilar.
- The Comparative Analytical Assessment submitted with the marketing application to support the demonstration of biosimilarity of the proposed product to the reference product should include lots of the proposed product used in principal clinical study (ies), as well as the proposed commercial product. A sponsor considering manufacturing changes after completing the initial comparative analytical assessment or after completing clinical studies may need to conduct additional comparative analytical studies of the proposed product (before and after change) and the reference product. The nature and extent of the changes may determine the extent of these additional analytical studies

➢ ***Considerations for Proposed Biosimilar Products:***

- It is recommended that a sponsor include multiple lots of the proposed product in the comparative analytical assessment, to ensure:
  1. Adequate characterization of the proposed product and understanding of manufacturing variability
  2. Adequate comparison to the reference product. These should include lots manufactured with the investigational- and commercial-scale processes, and may include validation lots, as well as product lots manufactured at different scales.

- To the extent possible, proposed biosimilar lots included in the comparative analytical assessment should be derived from different drug substance batches to adequately represent the variability of attributes inherent to the drug substance manufacturing process.

1. Quality Aspects:

A. Analytical consideration

1. Structural and Conformation Characterization

- A comprehensive set and combination of analytical methods are used, generally characterization tests include but not limited to:
- Primary Structures, such as amino acid sequence, N and C-terminal sequence. The target amino acid sequence of the biosimilar should be confirmed and is expected to be the same as for the reference medicinal product. The N- and C-terminal amino acid sequences, free SH groups and disulfide bridges should be compared, as appropriate.
- Higher order structures, including secondary, tertiary, and quaternary structure (including aggregation).
- Enzymatic Post-translational Modifications, such as glycosylation and phosphorylation. If present, carbohydrate structures should be thoroughly compared; including the overall glycan profile, site-specific glycosylation patterns as well as site occupancy. The presence of glycosylation structures or variants not observed in the reference medicinal product may raise concerns and would require appropriate justification, with particular attention to non-human structures (non-human linkages, sequences or sugars).
- Other Potential Variants, such as protein de-amidation and oxidation.
- Intentional Chemical Modifications, such as pegylation sites and characteristics.

2. Physicochemical Properties

- A physicochemical characterization program should include determination of the composition, physical properties, primary and higher order structures of the active substance of the biosimilar product.

- An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic process; therefore, the biosimilar product can contain a mixture of post-transnationally modified forms. Appropriate efforts should be made to investigate and identify these forms. The manufacturer should consider the concept of the desired product (and its variants) as defined in ICH Q6B when designing and conducting a comparability exercise. The complexity of the molecular entity with respect to the degree of molecular heterogeneity should also be considered.
- To address the full range of physicochemical properties or biological activities adequately, it is often necessary to apply more than one analytical procedure to evaluate the same quality attribute. Methods that use different physicochemical or biological principles to assess the same attribute are especially valuable because they provide independent data to support the quality of that attribute (e.g., orthogonal methods to assess aggregation). In addition, the use of complementary analytical techniques in series, such as peptide mapping or capillary electrophoresis combined with mass spectrometry of the separated molecules, should provide a meaningful and sensitive method for comparing products
- Particular analytical methodologies can be used to assess specific physicochemical characteristics of proteins. These methodologies are described in published documents, including scientific literature, regulatory guidelines, and international pharmacopeia. Some techniques provide information on multiple characteristics. *It is expected that appropriate analytical test methods will be selected based on the nature of the protein being characterized and knowledge regarding the structure and heterogeneity of the reference product and the proposed product, as well as characteristics critical to product performance.*

3. Biological activity

- An important property is the biological activity that describes the specific ability or capacity of a product to achieve a defined biological effect. A valid biological assay

(animals, cell culture, and/or ligand binding) to measure this activity shall be used by the manufacturer.

- The results of relevant biological assay(s) should be provided and expressed in units of activity calibrated against an international or national reference standard, where available and appropriate. If no such standards are available, an Internal Reference Standard must be established as per the ICH guidelines.
- These assays should comply with appropriate international Pharmacopoeia requirements for biological assays, if applicable.

4. Target Binding and Immunochemical properties

- They include but not limited to binding assays, affinity, avidity and immune-reactivity (including cross-reactivity).
- For some drug substances or drug products, the protein molecule may need to be examined using immunochemical procedures (e.g., ELISA, Western-blot) utilizing antibodies which recognize different epitopes of the protein molecule. Immunochemical properties of a protein may serve to establish its identity, homogeneity or purity, or serve to quantify it.
- When binding is part of the activity attributed to the protein product, analytical tests should be performed to characterize the proposed product in terms of its specific binding properties (e.g., if binding to a receptor is inherent to protein function, this property should be measured and used in comparative studies) (see ICH Q6B for additional details). Various methods such as surface plasmon resonance, microcalorimetry, or classical scatchard analysis can provide information on the kinetics and thermodynamics of binding. Such information can be related to the functional activity and characterization of the proposed product's higher order structure.

5. Purity and impurities

- The purity and impurity profiles of the proposed biosimilar product and reference medicinal product should be compared both qualitatively and quantitatively by a combination of analytical procedures.

- Appropriate State-of-the Art methods should be used to compare the product-related substances and impurities. This comparison should take into account specific degradation pathways (for example, oxidation, de-amidation, aggregation, truncation, charge variants, visible, sub-visible and sub-sub visible particle, etc…) of the biosimilar product and potential post-translational modifications of the proteins.
- Process-related Impurities arising from cell substrates (e.g., host cell DNA, host cell proteins), cell culture components (e.g., antibiotics, media components), and downstream processing steps (e.g., reagents, residual solvents, leachable, endotoxin, bioburden) should be evaluated. The process-related impurities in the proposed product are not expected to match those observed in the reference product and are not included in the comparative analytical assessment. Nevertheless, State-of-the-Art Analytical Technologies following existing guidelines and compendial requirements should be applied, and the potential risks related to these newly identified impurities (for example, immunogenicity) have to be appropriately documented and justified.
- The chosen analytical procedures should be adequate to detect, identify, and accurately quantify biologically significant levels of impurities. In particular, results of immunological methods used to detect host cell proteins depend on the assay reagents and the cell substrate used. Such assays should be validated using the product cell substrate and orthogonal methodologies to ensure accuracy and sensitivity.
- For product related impurities, the sponsor should characterize, identify, and quantify in the proposed product and the reference product, to the extent feasible. If a comparative physicochemical analysis reveals comparable product-related impurities at similar levels between the two products, pharmacological/toxicological studies to characterize potential biological effects of specific impurities may not be necessary. However, if the manufacturing process used to produce the proposed product introduces different impurities or higher levels of impurities than those present in the reference product, additional pharmacological/toxicological or other studies may be necessary. As discussed

in the ICH guidance for industry S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, "It is preferable to rely on purification processes to remove impurities . . . rather than to establish a preclinical testing program for their qualification".

B. <u>Specifications: Release of Drug Substance / Drug Product (DS / DP)</u>

- Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval to ensure product quality and consistency. They should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.
- The selection of tests to be included in the specifications is product specific and should be defined according to the ICH guidelines: Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products have to be consulted).
- Each acceptance criterion should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, and by data from lots used for the manufacturing process validation, data from stability studies, relevant development data and data obtained from the quality, safety and efficacy comparability exercise.
- The setting of specifications should be supported by global reasoning based on the applicant's experience of the biosimilar product (quality, safety and efficacy) and own experimental results obtained by testing the reference product. These data should demonstrate that the limits set for a given test are not wider than the range of variability of the representative RMP, unless justified.
- Methods used for setting specifications may or may not be the same as analytical methods used for product characterization and for establishing product comparability.

C. References standard

- If there is a suitable, publicly available and well-established reference standard for the protein, a physicochemical and/or functional comparison of the proposed product with this standard may also provide useful information. For example, if an international standard for calibration of potency is available, a comparison of the relative potency of the proposed product with this potency standard should be performed. As recommended in ICH Q6B, an In-House Reference Standard (s) should always be qualified and used for control of the manufacturing process and product.
- An in-house reference standard is typically developed from early development lots or lots used in a clinical study (ies). Ideally, a sponsor will have established and properly qualified primary and working reference standards that are representative of proposed product lots used in clinical studies that support the application.

D. Final Formulation

- The formulation of the biosimilar should be selected take into account state-of-the-art technology and, regardless of the formulation selected, the suitability of the proposed formulation with regards to stability, compatibility (i.e. interaction with excipients, diluents and packaging materials), integrity, activity and strength of the active substance should be demonstrated.
- The acceptability of the type, nature, and extent of any differences between the proposed finished biosimilar product and the finished reference product should be evaluated.

- Proteins are very sensitive to their environment. Therefore, differences in excipients or primary packaging may affect product stability and/or clinical performance. Differences in formulation and primary packaging between the proposed product and the reference product are among the factors that may affect whether or how subsequent clinical studies may take a selective and targeted approach.

- *Sponsors should clearly identify excipients used in the proposed product that differ from those in the reference product. The acceptability of the type, nature, and extent of any differences between the finished proposed product and the finished reference product should be evaluated and supported by appropriate data and rationale. Additionally, different excipients in the proposed product should be supported by existing toxicology data for the excipient or by additional toxicity studies with the formulation of the proposed product. Excipient interactions as well as direct toxicities should be considered.*

  - If a Different Formulation and/or Container/Closure system to the reference medicinal product is selected (including any material that is in contact with the medicinal product), its potential impact on the safety and efficacy should be appropriately justified.

A. <u>Stability</u>

Stability studies on both drug substance and drug product following "*ICH guidelines "Quality of biotechnology products: stability testing of biotechnological/biological products Q5C*" should be consulted.

- At time of submission, stability data on at least 3 Pilot Scale Batches can be provided with a Commitment to place the First 3 Manufacturing Scale Batches into the long-term stability program after approval.
- The quality of the pilot batches should be representative of the quality of the materials used in pre-clinical and clinical studies and of the quality of the materials made at production scale.
- Side-by-Side Accelerated and Stressed Studies comparing the biosimilar product to the reference product will be of value in determining the similarity of the products by showing comparable degradation profiles.
- Any claims with regard to stability and compatibility cannot be extrapolated from the reference product and must be supported by data.

- **<u>For local products</u>**, the applicant should submit *One year stability data* from the *Real Time Stability Study* for preliminary approval on stage 3 and submit *Full Long Term/Real time Stability Data* before issuing marketing authorization.
- **<u>For Imported product</u>**, *Long Term/ Real Time Stability Data* should be submitted for both *Drug substance and Drug product* to determine storage condition and shelf life.

2. Non-Clinical Studies

-To support Biosimilarity, relevant Comparative non-clinical Studies should be performed before initiating clinical trials. Analytical studies and in-Vitro Pharmaco-toxicological studies should be conducted first then take decision, if any, in-Vivo work in animal will be required.

- In non-clinical studies Sponsor should justify the selection of representative lots, including the number of lots. Sponsors analyze finished dosage form multiple lots of both products to assess Excipients and any formulation effect on the Purity, product- and process-related impurities, and stability. Differences in formulation between both products are among Factors that affect the extent and nature of subsequent animal or clinical testing.

- Sponsor Considering manufacturing changes after completing initial analytical similarity or after completing clinical testing that mean it should perform an additional analytical similarity assessment with lots manufactured by new process and establish comparability of proposed product manufactured by old and new manufacturing processes. The nature and extent of the changes may determine the extent of analytical similarity and comparability studies and any necessary additional studies.

2.1. Step 1 In-Vitro Studies:

-Non-Clinical in vitro studies should be performed with an appropriate number of batches of the reference product and of the biosimilar representative of the material intended for clinical use.

-In-Vitro Studies should be comparative in nature, sensitive and specific and sufficiently discriminatory to provide evidence that observed differences in quality attributes are clinically not relevant, some may already be available from quality-related assays (Structural and Functional assays), should be provided to compare the concentration–activity/binding relationship of the

biosimilar and the reference medicinal product at the pharmacological target(s), covering a concentration range where potential differences are most sensitively detected.

-These studies should include:

- Binding Assays (binding to receptors, antigens, enzymes) known to be involved in the pharmaco/toxicological effects and/or pharmacokinetics of the reference product.
- Signal Transduction and Functional Activity/Variability of cells that should be relevance for Pharmaco-toxicological effects of the reference product.
- *Assay used and Batch-to-Batch Variability will affect number needed*. The number tested should be sufficient to draw meaningful conclusions on the variability of a given parameter for both the biosimilar and the reference product and on the similarity of both products.
- Together, *these assays should cover the whole spectrum of pharmacological/toxicological aspects known to be of clinical relevance for the reference product and for the product class.*

2.2. Step 2 Determination of the need for In-Vivo Studies:

- Non-clinical evaluation in in vivo studies may be necessary to provide complementary information, provided that a relevant in vivo model with regard to species or design is available.

***Factors to be considered when the need for In-Vivo Non-Clinical Studies are evaluated, include, but are not restricted to*:**

- Presence of potentially relevant quality attributes that have not been detected in the reference product (e.g. new post-translational modification structures).
- Presence of potentially relevant quantitative differences in quality attributes between the biosimilar and the reference product.
- Relevant differences in formulation, e.g. use of excipients not widely used.

- -Although each of the factors mentioned above do not necessarily warrant in vivo testing, these issues should be considered together to assess the level of concern and whether there is a need for in vivo testing.

-If the Biosimilar Comparability Exercise for the physicochemical and biological characteristics and the Non-Clinical In Vitro Studies are considered satisfactory and no issues are identified in step 2 which would block direct entrance into humans, an in vivo animal study is usually not considered necessary.

-If Product-Inherent Factors that impact PK and/or bio-distribution, like extensive glycosylation, cannot sufficiently be characterized on a quality and in vitro level, in vivo studies may be necessary.

- The Applicant should carefully consider if the in vivo-studies should be performed in animals or as part of the clinical testing, e.g. in healthy volunteers.
- If there is a need for additional in vivo information, the availability of a relevant animal species or other relevant models (e.g. transgenic animals, transplant models) should be considered.
- If a relevant In Vivo Animal Model is not available, the applicant may choose to proceed to human studies taking into account principles to mitigate any potential risk.

2.3. Step 3 In-Vivo Studies:

- If an in vivo evaluation is deemed necessary, the focus of the study/studies (PK and/or PD and/or safety) depends on the need for additional information. Animal studies should be designed to maximize the information obtained.
- The principles of the 3Rs (replacement, refinement, reduction) should be considered when designing any in vivo study. Depending on the endpoints used, it may not be necessary to sacrifice the animals at the end of the study.
- The duration of the study (including observation period) should be justified, taking into consideration the PK behavior of the reference medicinal product and its clinical use.

- When the model allows and if not otherwise justified, the PK and PD of the biosimilar and the reference medicinal product should be *quantitatively compared, including, if feasible, a Dose Concentration-Response Assessment including the intended exposure in humans.*

2.3.1. Animal Toxicity Studies:

- For safety studies a flexible approach should be considered, in particular if non-human primates are the only relevant species. The conduct of standard repeated dose toxicity studies in non-human primates is usually not recommended. If appropriately justified, repeat dose toxicity with refined design (e.g: using just one dose level of biosimilar and Reference products and/or just one gender and /or no recovery animals) or *In-Life Evaluation of Safety Parameters (clinical signs , body weights , and vital function)* may be considered . If where only one dose to be evaluated, this would be selected *at the high end of the dosing range* and should be justified on basis of the expected toxicity of the Reference medicinal product.

- *Sponsor should identify appropriate scientific justifications for not conducting an animal toxicity study and for the scope and extent of such study.*

- If comparative Structural and Functional analyses data using the biosimilar product provide strong evidence for analytical similarity to Reference product may be sufficient to support initial clinical used of biosimilar product.

- If Structural and Functional data are limited or there are concerns about the biosimilar product quality, general toxicology study may needed that include full animal pathology,

histopathology, PK, PD and immunogenicity assessment. When the animal toxicology studies are conducted, it will be useful to perform *Comparative Bridging Toxicology* studies.

- The selection of *Dose*, regimen, duration, and test species for these studies should provide a meaningful toxicological comparison between the two products. It is important to understand the limitations of such animal studies (e.g., small sample size, intra-species variations) when interpreting results comparing the proposed product and the reference product.

- If no animal species that can provide pharmacologically relevant data for the product, animal data from a pharmacologically *Non Responsive Species* (including rodents) may be useful to support clinical studies with a proposed product that has not been previously tested in human subjects.
- If the animal toxicology studies are not warranted based on acceptable scientific justification, *Additional Comparative In-Vitro Testing* (Using human cells or tissues when appropriate) is needed.

2.3.2. Inclusion of animal PK/PD Measures:

- Under certain circumstances, a single-dose study in animals comparing the proposed product and the reference product using PK and PD measures may contribute to the totality of evidence that supports a demonstration of biosimilarity, PK and PD measures also can be incorporated into a single animal toxicity study, where appropriate.

2.3.3. Interpreting of Animal Immunogenicity:

- Although immunogenicity assessment in animals is generally not predictive for immunogenicity in humans, it may be needed for interpretation of *in vivo* studies in animals. Therefore, blood samples should be taken and stored for future evaluations of pharmacokinetic/toxicokinetic data if then needed.

- Differences in manufacturing process (e.g., impurities or excipients) or product-related variants between the proposed product and the reference product may affect biological functions of the biosimilar product and result in differences in immunogenicity, these differences are expected to be evaluated by appropriate *in vitro assays*, and measurement of *Anti-therapeutic Protein Antibody Responses* in animals may provide useful information that may reflect potential structural or functional differences between the two products not captured by other analytical methods.

- These differences and impurities may have an effect on immunogenic potential and the potential to cause hypersensitivity and should be further assessed in clinical trials.

2.3.4. Safety Pharmacology, Reproduction toxicology, Carcinogenicity and Genotoxicity: ***are not required*** **for non-clinical testing of Biosimilars.**

2.3.5. Local Tolerance:

- *Studies on local tolerance are usually not required*. However, if excipients are introduced for which are with no or little experience with the intended clinical route of administration may need to be evaluated and usually evaluated as part of repeat dose toxicity study instead of the performance of separate local tolerance studies.

3. Clinical Studies:

- The clinical biosimilar comparability exercise is normally stepwise procedure that should begin with comparative human PK and PD studies and a clinical immunogenicity assessment.
- In certain cases, the results of these studies may provide adequate clinical data to support a conclusion that there are no clinically meaningful differences between the proposed biosimilar product and the reference product. However, if residual uncertainty about biosimilarity remains after conducting structural, functional characterization, animal studies, human PK , PD studies and a clinical immunogenicity assessment, an additional comparative clinical study or studies would be needed to further evaluate whether there are clinically meaningful differences between the two products.

➢ ***Performing clinical studies should follow ICH guidelines taking into consideration some factors that may influence the type and the extent of comparative clinical study data needed:***

a. The nature and the complexity of the reference, the extensiveness of the structural and functional characterization, and the findings and the limitations of comparative structural, functional, and non-clinical testing, include the extent of observed differences.

b. The extent to which differences in structure, function, and non-clinical pharmacology and toxicology predict differences in clinical outcomes, in conjunction with the degree of understanding of the reference product and disease pathology

c. The extent to which human PK or PD is known to predict clinical outcomes (e.g., PD measures known to be relevant to effectiveness or safety, surrogate marker(s)), relevant examples include absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor (G-CSF), early viral load reduction in chronic hepatitis C to assess the effect of alpha interferons, glucose infusion rate in euglycaemic clamp test to compare two insulins and number of oocytes retrieved during in vitro fertilization for biosimilar follicle stimulating hormone. Magnetic resonance imaging of disease lesions can be used to compare two β-interferons in multiple sclerosis.

d. The extent of clinical experience with the reference product and its therapeutic class, including the safety and risk-benefit profile (e.g., whether there is a low potential for off-target adverse events), and appropriate endpoints and biomarkers for safety and effectiveness (e.g., availability of established, sensitive clinical endpoints).

e. The extent of any other clinical experience with the proposed product.

- Clinical data that required for the biosimilar is ***head to head*** comparability exercise with the reference product.

- *Clinical trials for biosimilars do not need to include all the pivotal studies conducted for the reference medicine to prove safety and efficacy in humans.*

- Comparative clinical trials are specifically designed to rule out clinically relevant differences in safety or efficacy between the biosimilar and the reference medicine, and to confirm biosimilarity.

- All clinical studies of the proposed biosimilar product should be performed using ***materials from the final manufacturing process expected to be used in the market product if approval is granted.***

- The relevance of data submitted from using materials from different manufacturing processes may need to adequately justified by establish an analytical and PK bridge to the to-be-marketed Product.

3.1-Pharmacokinetic Studies:

- Comparative pharmacokinetic (PK) studies designed to demonstrate similar PK profile of the Biosimilar and the reference medicinal product with regard to key PK parameters are an essential part of the biosimilar development program.

- The design of a PK study depends on various factors, including clinical context, safety, PK characteristics of the reference product (target-mediated disposition, linear or non-linear PK, time dependency, half-life, etc.)

3.1.1.PK measures :

- All Pk measures should be obtained for both the Biosimilar product and the Reference product.

Single Dose Pk Study		
	IV	SC
Primary endpoints	-AUC $_{(0\text{-inf})}$	-AUC $_{(0\text{-inf})}$ -C_{max}
Secondary endpoints	-T_{max} -Vd : Volume of distribution -$T_{1/2}$: Half-life	
Other mandatory endpoints	Anti-drug antibodies should be measured in parallel to PK assessment using appropriate sampling time points.	

Multiple Dose Pk Study	
Primary endpoints	-$AUC_{0\text{-}tau}$: Truncated area under the curve after the first administration until the second administration. -AUC I : area under the curve over dosage interval at steady state.
Secondary endpoints	-C_{max} -C_{trough} at steady state
Other mandatory endpoints	-Anti-drug antibodies should be measured in parallel to PK assessment using appropriate sampling time points.

3.2- Pharmacodynamic Studies:

- A human PD study that demonstrates a similar effect on a relevant PD measure(s) related to effectiveness or specific safety concerns (except for immunogenicity, which is evaluated separately) represents even stronger support for a biosimilarity determination.

- It is recommended that pharmacodynamic (PD) markers are added to the pharmacokinetic studies whenever feasible. *The PD markers should be selected on the basis of their relevance to the clinical outcome.*

- The PD biomarker(s) used to measure PD response should be a single biomarker or a composite of biomarkers that effectively demonstrate the characteristics of the product's target effects. Use of scientifically appropriate PD biomarker can reduce residual uncertainty regarding the existence of any clinically meaningful differences between products and can significantly add to the overall demonstration of biosimilarity.

➢ ***When determining which biomarkers should be used to measure response, it is important to consider the following five characteristics:***

- The *time of onset* of change in the PD biomarker relative to dosing and its return to baseline with discontinuation of dosing.
- The *dynamic range* of the PD biomarker over the exposure range to the biological product.
- The *sensitivity* of the PD biomarker to differences between the proposed biosimilar product and the reference product.
- The *relevance* of the PD biomarker to the mechanism of action of the drug (to the extent that the mechanism of action is known for the reference product).
- The *analytical validity* of the PD biomarker assay.
- In some instances, PD biomarkers with the relevant characteristics listed above are not identified, but the sponsor is still encouraged to incorporate PD biomarkers that achieve a large dynamic range over the concentration range in the PK evaluation because these PD biomarkers represent potential orthogonal tests that can support similarity.

- When PD biomarkers are not sensitive or specific enough to detect clinically meaningful differences, the derived PK parameters should be used as the primary basis for evaluating similarity from a clinical pharmacology perspective, and the PD biomarkers can be used to augment the PK data.

- *A combination of PK and PD similarity can be an important assessment in demonstrating that there are no clinically meaningful differences between the proposed biosimilar product and the reference product.*

-In certain cases, comparative PK/PD studies may be sufficient to demonstrate clinical comparability of the biosimilar and the reference medicinal product, provided that the following conditions are met:

- The selected PD marker/biomarker is an accepted surrogate marker and can be related to patient outcome to the extent that demonstration of similar effect on the PD marker will ensure a similar effect on the clinical outcome.
- Relevant examples include: absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor (G-CSF), early viral load reduction in chronic hepatitis C to assess the effect of alpha interferons, and euglycaemic clamp test to compare two insulins. Magnetic resonance imaging of disease lesions can be used to compare two β-interferons in multiple sclerosis.
- There may be PD-markers that are not established surrogates for efficacy but are relevant for the pharmacological action of the active substance and a clear dose-response or a concentration response relationship has been demonstrated.

- **In some of these cases,** *a single or multiple dose-exposure response study at two or more dose levels may be sufficient to waive a clinical efficacy study*.

- **In exceptional cases**, *the confirmatory clinical trial may be waived if physicochemical, structural and in vitro biological analyses and human PK studies together with a combination of PD markers that reflect the pharmacological action and concentration of the active substance can provide robust evidence for biosimilar comparability.*

- **If the biosimilar comparability exercise indicates that there are relevant differences between the biosimilar and the reference medicinal product,** *making it unlikely that biosimilarity will eventually be established, a Stand-Alone Development to support a full Marketing Authorization Application should be considered instead.*

3.2.1. PD measures:

- Assessment of Biosimilarity should be based on similarity in PD using biomarkers that reflect the mechanism of drug action when PD measure has wide dynamic range over the

range of the drug concentrations achieved during PK study. In such instances, full evaluation of safety and immunogenicity should still conducted.

- Selection of time points and durations for the measure of PD biomarkers will depend on the characteristics of PD biomarkers (e.g.: Timing of PD response after administration of product based on half-life of the product and the anticipated duration of the product's effect).

- When PD response lags after initiation of Product administration, a study of multiple dose and steady state conditions can be important, especially if the proposed product is intended for long-term use. The PD biomarkers evaluated for biosimilar product and the reference should be compared by determining area under the effect cure (AUEC).

- If only one PD measurement is available because of the characteristics of the PD biomarker, the measurement should be linked to a simultaneous drug concentration measurement. The relationship of drug concentration and the PD biomarker should then be used as a basis for comparison between products.

- When available and appropriate, clinical endpoints in clinical pharmacology studies can also provide useful information about the presence of clinically meaningful differences between two products.

➢ ***<u>The following aspects should be fulfilled for demonstration of Clinical PK and PD Similarity:</u>***

A- Study Design:

-There are two designs are available: *Cross-Over Design and Parallel Design.*

Cross-Over Design	Parallel Design
- Single dose , Randomized study which recommended for product with short half-life (shorter than 5 days) , rapid PD response (e.g.: Time of onset , maximal effect , and disappearance in conjugation with drug exposure) , and low incidence of immunogenicity. - Should include full characterization of PK profile, late elimination phase. - This design is considered the most sensitive to assess PK similarity - For PD similarity, use multiple dose design may be appropriate when PD effect is delayed or not parallel to single-dose drug PK profile. - The time of appearance and disappearance of immunogenicity and its relation to washout period should be considered using this type of study design.	- It is Appropriate for Biological products have long half-life and elicit immunogenic response (especially for products where repeated exposure can lead to increase immunogenicity) that can effect on PK/PD biosimilarity assessment. - This design is also appropriate for diseases that exhibit time-related changes associated with exposure to drug.

- A clinical study or studies designed to establish statistical evidence that the proposed product is neither inferior to the reference product by more than a specified margin nor superior to the reference product by more than a (possibly different) specified margin.

- A well-designed clinical PK and PD study should include information about the *Exposure* and, when possible, the *Exposure-Response* to the biological products, which are important for assessing whether there are any potential clinically meaningful differences between two products.

- Determining the exposure-response to a biological product can be particularly challenging because of the complex nature and heterogeneity of biological products. An evaluation of clinical pharmacology similarity should include assessments of PK similarity, and if applicable, PD similarity.

B- Dose Selection:

- The most sensitive dose should be selected to detect and to evaluate differences in the PK and PD profiles between the proposed biosimilar product and the reference product should be one most likely to provide clinically meaningful and interpretable data.

➢ ***Criteria for Dose selection:***

1- If a study is conducted in a *Patient Population*, the approved dose for the reference product can be the appropriate choice, because this approved dose can best demonstrate the pharmacological effects in a clinical setting.

2- A lower dose on the steep part of the exposure-response curve is generally appropriate when PD is being measured or when *Healthy Subjects* are selected for evaluation

(Studying doses on the Plateau of the dose response curve is unlikely to detect clinically meaningful difference between two products).

3- In certain cases, a dose selected from a range of doses can be useful for a clinical PK and PD similarity assessment. For example, if the concentration-effect relationship of the reference product is known to be highly variable or nonlinear, a range of doses can be used to assess dose response.

4- If the product can only be administered to patients, an alternative dosing regimen such as a single dose for a chronic indication or a lower dose than the approved dose may be preferable to increase the sensitivity for detecting differences if the approved dose either results in nonlinear PK or exceeds the dose required for maximal PD effect. The appropriateness of an alternative dosing regimen will depend on certain factors, e.g., whether the lower dose is known to have the same effect as the approved dose and whether it is ethically appropriate to give lower doses notwithstanding differences in effect.

An adequate justification for the selection of an alternative dosing regimen should be provided.

C-Routes of administration:

- Clinical PK and PD studies should be conducted using the same route of administration for the proposed biological product and the reference product. If the reference product can be administered both intravenously and subcutaneously, the evaluation of subcutaneous administration will usually be sufficient as it covers both absorption and elimination. Thus it is possible to waive the evaluation of intravenous administration if biosimilar comparability in both absorption and elimination has been demonstrated for the subcutaneous route or other extravascular routes. Omission of the PK study of intravenous administration needs to be justified, e.g., in cases when the molecule has absorption constant which is much slower than the elimination constant (flip flop kinetics).

D-Study Population:

-The total number of subjects studied should provide adequate statistical power for PK, and, when relevant, PD similarity assessment.

-The choice of study population *(Healthy subjects or Patient)* should allow for an assessment of clinically meaningful differences between the proposed product and the reference product; often the study population will have characteristics consistent with those of the population studied for the licensure of the reference product for the same indication.

-However, there are cases where a study population could be different from that in the clinical studies that supported the licensure of the reference product. For example, if a genetic predictor of response was developed following licensure of the reference product, it may be possible to use patients with the response marker as the study population.

Healthy Subjects vs. Patient:	
Healthy subjects	**Patients**
-Clinical PK and PD should be conducted in healthy subjects if the product can be safely administered to them. -Healthy subjects is considered to be more sensitive in evaluating the product similarity because it is likely to produce less PK and/or PD variability compared with study in patients with potential confounding factors such as concomitant disease and concomitant medications .	-If safety or ethical consideration prevent participation of healthy subjects in such studies for certain products (immunogenicity or known toxicity from Reference) or if PD biomarkers can only be relevant in patients with the relevant condition or disease, the clinical pharmacology studies should be conducted in such patients.
Demographic group Clinical pharmacology studies should be conducted in subjects or patients demographic group (e.g.: Gender, Age, Race, marital state, etc.) most likely to provide a sensitive measure of difference between biosimilar and the Reference product.	

-The sponsor should justify why the subject or patient group chosen for studies will provide adequately sensitive measure of difference between two products.

E-Statistical Comparison of PK and PD results:

- The assessment of the clinical pharmacology similarity of a proposed biosimilar product and the reference product in PK and PD studies is based on statistical evaluation. The recommended clinical pharmacology similarity assessment relies on:
- A criterion to allow the comparison.
- A confidence interval for the criterion, and (3) an acceptable limit for the biosimilarity assessment.

- Sponsors should use an *Average Equivalence Statistical Approach* to compare PK and PD parameters for both replicate and non-replicate design studies. This average equivalence approach involves a calculation of a 90% confidence interval for the ratio between the geometric means of the parameters of the proposed biosimilar product and the reference product.

- To establish PK and/or PD similarity, the calculated confidence interval should fall within an acceptable limit. Selection of the confidence interval and the acceptable limits can vary among products. An appropriate starting point for an acceptable limit for the confidence interval of the ratio is 80–125%; if other limits are proposed, the sponsor should justify the limits selected for the proposed biosimilar product.

- There can be situations in which the results of the PK and/or PD study fall outside the pre-defined limits, that can suggest existence of differences between the proposed biosimilar product and the reference product, the sponsors should analyze and explain such findings.

3.3 Efficacy trails:

- In the absence of surrogate markers for efficacy, it is usually necessary to demonstrate comparable clinical efficacy of the Biosimilar and the Reference medicinal products in adequately powered, *Randomized, Parallel Comparative* clinical trial(s), preferably *Double Blind* by using efficacy endpoints. Comparability should be demonstrated in appropriately sensitive clinical models and study conditions.

- The *Study Population* should be generally representative of the approved therapeutic indication(s) of the reference and sensitive for detecting potential differences between Biosimilar and the Reference.

3.3.1 Study Design:

- In general, an equivalence design should be used, the use of a non-inferiority design may be acceptable if justified on the basis of a strong scientific rationale and taking into consideration the characteristics of the reference product, e.g. (safety profile/tolerability, dose range, dose-response relationship).

- *A Non-Inferiority Trial may only be accepted where the possibility of significant and clinically relevant increase in efficacy can be excluded on scientific and mechanistic grounds. However, as in equivalence trials, assay sensitivity has to be considered.* ***It is recommended to discuss the use of a non-inferiority design with regulatory authorities.***

3.3.2 Efficacy Endpoints:

- The purpose of the efficacy trials is to confirm comparable clinical performance of the biosimilar and the reference product.

- Comparability should be demonstrated in appropriately sensitive clinical models and study conditions.

- The applicant should justify that the chosen model is relevant and sensitive to detect potential differences with regard to efficacy and safety. Nevertheless, *deviations from endpoints recommended in disease-specific guidelines need to be scientifically justified.*

- The correlation between the “hard” clinical endpoints recommended by the guidelines for new active substances and other clinical/pharmacodynamic endpoints that are more sensitive to detect clinically meaningful differences may have been demonstrated in previous clinical trials with the reference product.

- **In this case**, *it is not necessary to use the same primary efficacy endpoints as those that were used in the marketing authorisation application of the reference product. However, it is advisable to include some common endpoints (e.g. as secondary endpoints) to facilitate comparisons to the clinical trials conducted with the reference product.* ***Comparability margins should be pre-specified and justified on both statistical and clinical grounds by using the data of the reference product.***

3.4 Clinical safety:

- Clinical safety is important throughout the clinical development program and is captured during initial PK and/or PD evaluations and also as part of the pivotal clinical efficacy study. Comparative safety data should normally be collected pre-authorization to characterize the safety profile of Biosimilar product.

- Comparison with the Reference should include Type, Frequency, and Severity of adverse events/reactions. The duration of safety follow-up pre-authorization should be justified. Care should be given particularly to adverse events those described in SmPC of the Reference product.

- The application dossier should include an evaluation of the specific risks anticipated for the biosimilar. This includes in particular a description of possible safety concerns that may result from a manufacturing process different from that of the reference product, especially those related to infusion-related reactions and immunogenicity.

Immunogenicity:

- The goal of clinical immunogenicity assessment is to evaluate potential differences between the proposed product and the Reference products in the incidence and the severity of human immune responses that affect both the safety and the effectiveness of the product, for example, altering PK, inducing anaphylaxis, or promoting development of neutralizing antibodies that neutralize the product.

- Structural, functional, and animal data are generally not adequate to predict immunogenicity in humans. Therefore, at least one clinical study that includes a comparison of the immunogenicity of the proposed product to that of the reference product is recommended.

- The overall immunogenicity assessment should consider the nature of the immune response (e.g., anaphylaxis, neutralizing antibody), the clinical relevance and severity of consequences (e.g., loss of efficacy of life-saving therapeutic and other adverse effects), the incidence of immune responses, and the relevant population being studied that are not immunocompromised and thus are able to mount an immune response.

- Using comparative blinded, parallel design (i.e., a head-to-head study) in treatment-naïve patients as the most sensitive design for pre-marketing study to assess potential differences in the risk of immunogenicity is recommended. The proposed Biosimilar product and the Reference should be assessed using the same assay with the same patient sera level whenever possible.

- If a sponsor is seeking to *extrapolate immunogenicity findings* for one condition of use to other conditions of use, the sponsor should consider using a study population and treatment regimen that are adequately sensitive for predicting a difference in immune responses between the proposed product and the reference product across the conditions of use. Usually, this will be the population and regimen for the reference product for which development of immune responses with adverse outcomes is most likely to occur.

- ***Duration of the immunogenicity study should be justified on case-by-case basis depending on the duration of treatment course, disappearance of the product from circulation and the time for emergence of humoral immune response (at least four weeks when an immunosuppressive agent is used).***

- The extent and timing of clinical immunogenicity assessment will vary depending on range of factors:

- Extent of analytical similarity.
- Incidence and clinical consequences of immune Reponses for reference (If Consequences is *Severe* , more extensive immunogenicity assessment will needed / If immune response to reference is *Rare* , pre-marketing evaluation may be adequate to support similarity / In addition, in some cases, Certain safety risks may need to be evaluated through post-marketing surveillance).

- The differences in immune responses between both products in absence of observed clinical sequelae may be of concern and may need further evaluation (extended period of Follow-up evaluation).

- The follow up period is recommended to be 1 year unless a shorter period can be justified based on totality evidence to support biosimilarity).Shorter follow up data pre-authorized (6 months) might be justified based on the immunogenicity profile of the Reference. If needed, immunogenicity data for an additional period, up to one-year, could then be submitted post-authorization.

➢ ***The Duration of follow-up evaluation should be determined based on:***

(1) The time course for the generation of immune responses (such as the development of neutralizing antibodies, cell-mediated immune responses).

(2) Expected *clinical sequelae* (informed by experience with the reference product).

(3) The time course of disappearance of the immune responses and clinical sequelae following cessation of therapy.

(4) *The length of administration of the product. For example, for chronically administered agents, the follow-up period is recommended to be 1 year unless a shorter duration can be scientifically justified based on the totality of the evidence to support biosimilarity*.

- Sponsor should evaluate the following antibody parameters: Titer, Specifity, Relevant Isotype Distribution, Time course of development, Persistence, Disappearance, Impact on PK, Association with the clinical sequelae, and Neutralization of product activity.

  - *If lower immunogenicity for Biosimilar is possible, this would not preclude approval as a biosimilar. In case of reduced development of neutralizing antibodies with the biosimilar that suggest that the biosimilar is more effecious that the Reference product. It is recommended to pre-specify an additional subgroup analysis of efficacy and safety in those patients that did not mount an anti-drug antibody response during the clinical trial. This will be helpful to establish efficacy of the biosimilar and the Reference product in principle similar if not impacted by immune response.*

3.3.3 Extrapolation of Efficacy and Safety from one therapeutic indication to another:

- The reference medicinal product may have more than one therapeutic indication. When biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable, but needs to be scientifically justified.

- In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data will be required. Extrapolation should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data.

- It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physico-chemical and structural analyses as well as by *in vitro* functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication.
- ***Additional data are required in certain situations, such as:***
- The active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indications.
  2. The active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications.
  3. The studied therapeutic indication is not relevant for the others in terms of efficacy or safety, i.e. is not sensitive for differences in all relevant aspects of efficacy and safety.

- Immunogenicity is related to multiple factors including the route of administration, dosing regimen, patient-related factors and disease-related factors (e.g. co-medication, type of disease, immune status). Thus, immunogenicity could differ among indications. Extrapolation of immunogenicity from the studied indication/route of administration to other uses of the reference product should be justified.

VIII. Pharmacovigilance

- The guidance provided in this part is addressing only Pharmacovigilance requirements in context of registration of biosimilar biological products. For details, regarding these Pharmacovigilance requirements and the other Pharmacovigilance requirements throughout product life cycle refer to the *Good Pharmacovigilance Practice for Arab Countries* (GVP-Arab) guideline which should be read in parallel with this guideline.

- Within the authorization procedure the applicant should demonstrate adequate pharmacovigilance system and adequate risk management plan in place in accordance with current Pharmacovigilance guideline.

- The risk management plan should take into account identified and potential risks associated with the use of the reference product and should detail how these issues will be addressed in post-marketing follow-up.

- Risk minimization activities in place for the reference medicinal product should, in principle, also be included into the risk management program of the biosimilar. Any deviation from this (e.g. when the risk minimization is linked to the device used with the reference product) should be justified

- Immunogenicity should specifically be addressed in this context and reflected in the RMP. Any specific safety monitoring imposed on the reference medicinal product or product class should be adequately addressed in the pharmacovigilance plan of the biosimilar.

- Any product specific immunogenicity risk and/or proposed difference in the safety specification of the biosimilar compared to the reference product should be adequately justified based on the comparability exercises, and must be addressed in the RMP and cover by Pharmacovigilance and/or risk minimization activities.

- In addition product specific immunogenicity risk must be reflected in the RMP and also should be covered by Pharmacovigilance and/or risk minimization activities.

- For *Imported biosimilars*; the applicant should demonstrate safety information from post marketing experience in other countries (in form of PBRER).

IX. Glossary

ADME: Absorbtion, Distribution, Metabolism, Elimination

ASMF: Active substance master file

CAPA: Central Administration for Pharmaceutical Affairs

CMC: Chemistry, Manufacturing and Control

EPVC: Egyptian Pharmacovigilance Center

ICH: International Conference on Harmonisation

NORCB: National Organization for Research and Control of Biologicals

PD: Pharmacodynamic

PK: Pharmacokinetic

PSUR: Periodic Safety Update Report

PBRER: Periodic Benefit-Risk Evaluation Report

RMP: Risk management plan

SMF: Site Master File

MA: Market Authorization

QTPP: Quality Target Product Profile

Reference guidelines and their updates

- WHO- GUIDELINES ON EVALUATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS
- ICH guidelines
  - ICH S6- Pre-clinical safety Evaluation of Biotechnology-derived pharmaceuticals
  - ICH E8- General consideration for clinical trials
  - ICH E9- Statistical principles for clinical trials
  - ICH Q5C - Quality of Biotechnological products: Stability testing of Biotechnological/Biological products
  - ICH Q5D - Derivation and characterization of cell substrates used for production of Biotechnological/Biological products
  - ICH Q5A - Viral safety evaluation of Biotechnology products derived from cell lines of human and Animal origin
  - ICH Q5B Quality of biotechnological products: analysis of the expression construct in cells used for production of r-DNA derived protein products
  - ICH Q5E - Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process
  - ICHQ8(R2) Pharmaceutical Development
  - ICH Q9 Quality Risk Management
  - ICH Q10 Pharmaceutical Quality System
  - ICH Q11- Development and manufacture of drug substances (chemical entities and biotechnological/biological entities
- **EMA**-Overarching biosimilar guidelines
- **EMA**- Product-specific biosimilar guidelines
- **EMA**- GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS
- **EMA**- Other guidelines relevant for biosimilars
- **EMA**- Scientific Guidelines on Biological Drug substances
- **EMA**- Scientific Guidelines on Biological Dug Products
- **FDA**- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

- **FDA**- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
- FDA- Comparative Analytical Assessment and Other Quality-Related Considerations
- FDA- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product
- ICH guidelines: Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
- League of Arab States. Guideline on good pharmacovigilance practices (GVP) for Arab countries.
- The Egyptian Pharmaceutical Vigilance Centre. Guidelines. Ministry of Health and Population. http://www.epvc.gov.eg/guidelinesmd.