# Guidelines For Registration of Biosimilar Products In Egypt.



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# Contents





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## Introduction

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

The Aim of the Biosimilar approach is to demonestrate close similarity of the biosimilar product in terms of quality, safety and efficacy to a selected reference medicinal biological product.

A high degree of similarity between the proposed biosimilar and the reference product is the basis for reduced pre-clinical and clinical package for registeration through an abbreviated pathway.

## I. 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.



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## II. Scope

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

## III. 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.

**Production 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.

**Equivalence study:** A trial with the primary objective of showing that the response to two or more treatments differs by an amount which is clinically unimportant. This is usually achieved by demonstrating that the true treatment difference is likely to lie between a lower and an upper equivalence margins of clinically acceptable differences.

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



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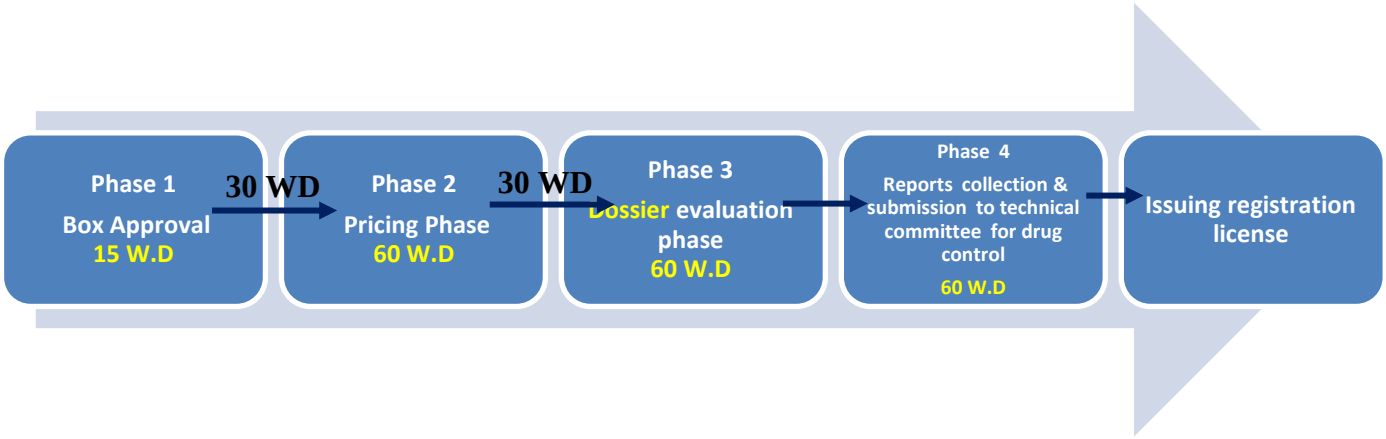
## IV. Registration of a biosimilar product

Two approaches are applied for registration of biosimilar products:

### 1. For Imported products:

The finished product is manufactured and marketed in the country of origin and only evaluation of the final dossier is performed. The steps of registration are as follows:




In the box: authority time frame

On the arrow: applicant time frame

### 2. For locally manufactured products:

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

a) Manufacturing finished product starting from developing active substance to the final finished product in local factory/factories

b) Manufacturing finished product starting from manufacturing the final formulation from an imported active substance.

c) Filling of an imported ready to fill final bulk..

**For case a) and case b) the following registration workflow should be followed:**



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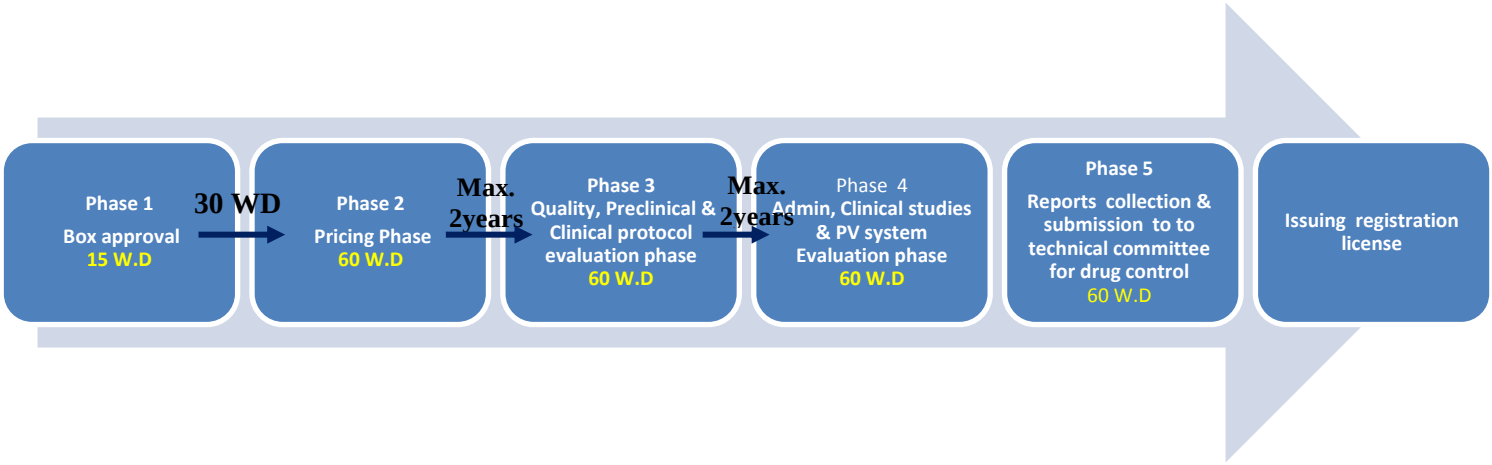


- ***Phase 1*:** The applicant submits an application inquiry for box approval, box approval or disapproval is issued within 15 W.D, if the box is opened, the following phases/steps have to be completed
- ***Phase 2*:** The applicant submits the pricing dossier within 30 W.D of receiving box approval
- Pricing license is issued within 60 W.D with 2 years validity period
- 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 and inspection of the site from inspection department before starting development process).*
    - The applicant has to develop the biosimilar product, perform the quality and preclinical comparability studies along with the preparation of clinical studies protocol. At the end, the results of quality and preclinical studies as well as the clinical studies protocol are submitted for evaluation.
- ***Phase 3*:** An assessment of the submitted quality and preclinical comparability studies is performed by the regulatory authority and approval on clinical studies protocol is issued for the applicant to perform clinical studies with 2 years validity period.
- After completion of the clinical studies, the applicant completes the registration dossier to be submitted for validation and assessment.
- ***Phase 4*:** An assessment of registration dossier is performed during this phase and the final assessment report is issued within 60 W.D
- ***Phase 5*:** Reports collection for submission to Technical committee for drug control within 60 W.D.



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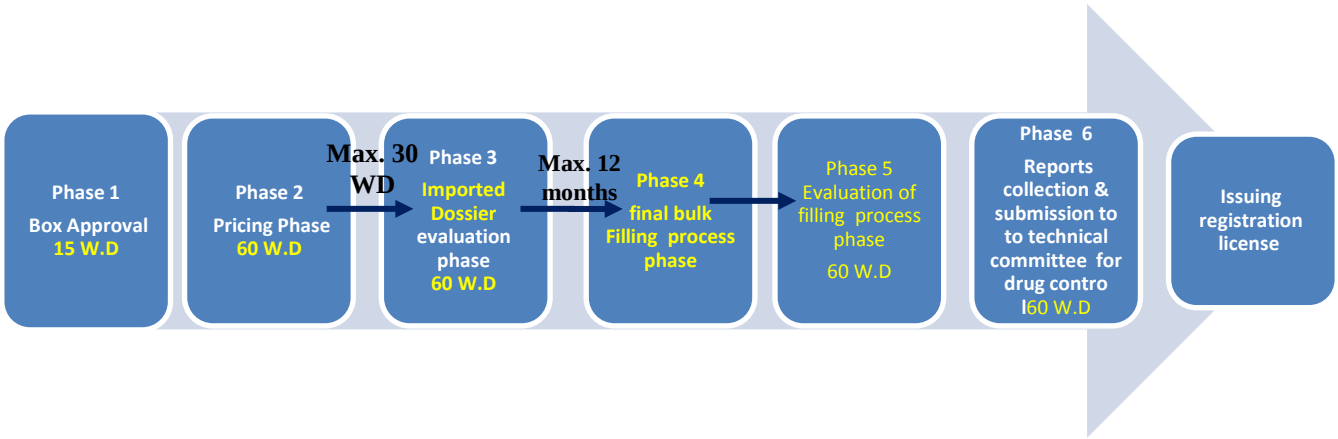
**For case c) the following registration workflow should be followed:**




**N.B: All requirements for registration of imported product should be fulfilled.**

**- Phase 4:** ( 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.

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.

## V. 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 master file 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:**

- Same reference product should be used for all parts of the dossier to demonstrate that biosimilar and the reference product have similar profiles in terms of quality, safety and efficacy in order to allow the generation of coherent data and conclusions.



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- **The reference product should fulfill the following criteria:**

  - Drug substance of the reference biological product and that of the biosimilar product must be be similar.
  - The primary structure of the drug substance of the reference biological product and that of the biosimilar product must be identical.
  - **The reference biological product** should be authorized on basis of complete dossier (full Quality, Preclinical and Clinical data). Therefore an approved biosimilar cannot be considered as a reference product.
  - It should be either Licensed in Egypt or licensed and widely marketed in a reference country for at least 2 years at time of submission and 4 years at time of acquiring registration license.*(N.B: in case the reference product is not licensed in Egypt the company shall provide samples from the reference product together with the reference standard and the samples of the proposed biosimilar product for analysis)*
  - It should have the same dosage form, strength, and route of administration of the biosimilar product intended to be developed.

**2- Manufacturing Process and Expression system:**

- The development and documentation for biosimilars should cover two distinct but complementary aspects:
  i) The molecular characteristics and quality attributes (QA) of the target product profile should be comparable to those of the reference medicinal product;
  ii) The performance and consistency of the manufacturing process of the biosimilar should be achieved on its own.

- The quality of 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.
- The QTPP should be detailed at an early stage of development and forms the bases for the development of the biosimilar product and its manufacturing process. It is important to identify critical quality attributes that may impact the safety and efficacy of the product.
- In case of developing recombinant products, it is expected that the expression construct for a proposed biosimilar product will encode the same primary amino acid sequence as its reference product. *(For example, somatropin produced in yeast cells appears to have similar characteristics to somatropin expressed in E. coli.)*



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- The use of novel expression systems should be carefully considered, as they may introduce additional risk, such as atypical glycosylation pattern, higher variability or even a different impurity profile, as compared to the reference medicinal product.
- The expression of the active substance of the biosimilar product in the same host cell type of the reference product is expected to produce a product that will encode the same primary amino acid sequence.
- If the manufacturer used host cell type different from that of the reference biological product for development of a biosimilar product, more extensive comparability exercise should be employed to assure quality, efficacy and safety of the biosmilar product.
- However, demonstration of comparability for glycoproteins will be difficult because glycosylation patterns vary significantly between different host cell types.
- 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.*

## VI. Comparability Key elements

- It is recommended to generate the comparability quality, preclinical and clinical data between the biosimilar product and the reference biological product using the product manufactured with the final manufacturing process, If changes are introduced to the active substance and/or the finished product during the product development, comparability assessment for the biosmilar product before and after change should be performed as per ICH guidelines Q5E - Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process.
- 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.
- Data from suitable number of batches, at least 3 pilot scale batches of the proposed biosimilar product at time of submission should be provided for proving similarity with the reference product.



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- Complete CMC data should be submitted in CTD format according to ICH guidelines in addition to quality comparability exercise with the reference product.
- Preclinical and clinical comparative studies with the same reference product used in the quality comparability exercise should be submitted. The extent of the preclinical and clinical data required depends mainly on the outcomes of the quality data *(for example differences in impurities or excipients may have a potential impact on clinical safety and efficacy of the biosimilar product and a justification for allowing such differences should be provided).*
- 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 biodistribution of the product and thereby change the dosing scheme, then this product cannot be considered a biosimilar product.).*

## 1- Quality Aspects:

Level of comparability studies (drug substance and drug product level):

- Product characterization studies for both the proposed biosimilar and the reference biological medicinal product should be performed using state of the art analytical methods.
- If the drug substance of the reference biological medicinal product is available, comparability exercise should be performed on both drug substance and drug product level, but due to general unavailability of the drug substance of the reference biological product, comparability exercise is generally performed on the finished 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. If applicable, standards and reference materials (*for example, from Ph. Eur., WHO*) should be used for method qualification and standardization.

- 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 *(for example, due to the low concentration of active substance and/or the presence of interfering excipients such as albumin)*. In such cases, samples could be prepared from the finished product *(for example extraction, concentration by suitable techniques)*. Where such preparation techniques are used, the preparation procedures should be outlined, and the impact of the sample preparation process should be appropriately documented and discussed (*for example, comparison of active substances before and after formulation/deformulation preparation).*



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**A. 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.
  - Higher order structures, including secondary, tertiary, and quaternary structure (including aggregation).
  - Enzymatic post-translational modifications, such as glycosylation and phosphorylation.
  - Other potential variants, such as protein deamidation and oxidation.
  - Intentional chemical modifications, such as pegylation sites and characteristics.

**B. Specifications: Release of drug substance /drug product (DS / DP)**

- Appropriate analytical test methods should be selected based on the nature of the protein being characterized and knowledge regarding the structure and heterogeneity of the reference and the proposed biosimilar product (ICH guidelines: Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products have to be consulted)
- Specifications for the proposed biosimilar product should be set based on the applicant's own experimental results obtained for both the proposed biosimilar and the reference product.
- Specifications should not be wider than the range of variability of the reference product, unless justified.
- 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 demonstration of manufacturing consistency, data from stability studies, relevant development data and data obtained from the comparability exercise.
- Methods used for setting specifications may or may not be the same as analytical methods used for product characterization and for establishing product comparability.

<u>This comparability testing regarding specifications includes:</u>

- **Physicochemical properties**

  They include but not limited to molecular weight/size , isoform pattern , extinction coefficient, electrophoretic patterns, liquid chromatographic patterns, spectroscopic profiles.

- **Biological activity (potency)**

  Appropriate biological assays are required to characterize the activity and establish the product's mechanism of action and clinical effects (in units of activity).



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Assays should be 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 European Pharmacopoeia requirements for biological assays, if applicable.

It includes but not limited to animal-based biological assays, cell culture-based bioassays, biochemical and biophysical assays.

- **Immunochemical properties**

  They include but not limited to binding assays of the antibody to antigen, affinity, avidity and immune-reactivity (including cross-reactivity).

- **Purity and impurities**

  - The purity and impurity profiles of the active substance and 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, deamidation, 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.
  - 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.
  - Process-related impurities *(for example, host cell proteins, host cell DNA, reagents, downstream impurities)*, They are expected to differ qualitatively from one process to another, and therefore, the qualitative comparison of these parameters may not be relevant in the comparability exercise (may not form a part of the comparability exercise; however they must be controlled as a part of biosimilar manufacture).
  - 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.



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**C. Final formulation**

- The formulation of the biosimilar does not need to be identical to that of the reference medicinal product. The applicant should 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.
- 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 biosimilar product.
- Excipient interactions as well as direct toxicities should be considered. Proteins are very sensitive to their environment, therefore, differences in excipients or primary packaging may affect product degradation and/or clinical performance.
- 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.
- Differences in formulation between the proposed biosimilar product and the reference product are among the factors that may affect whether subsequent clinical studies may take a selective and targeted approach.

"Release tests should be validated according to the ICH guideline: *Q2 (R1) Validation of analytical procedures: text and methodology*. If available, standards and reference materials (*(for example, from Ph. Eur., WHO, etc*.) should be used for method qualification and validation".

**D. Stability**

- Stability studies on both drug substance and drug product following "*ICH guidelines "Quality of biotechnology products: stability testing of biotechnological/biological products QC5*" should be consulted. At time of submission, stability data for 6 months as minimum on at least 3 pilot scale batches can be provided with a commitment to place the first three 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.



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## 2- Preclinical Aspects

The design of an appropriate pre-clinical study program requires a clear understanding of the product characteristics outcomes from the quality comparability data and depends on the product class. Generally the spectrum of studies required to establish safety & efficacy of the biosimilar product may vary considerably & should be defined on a case-by-case basis.

**A. Factors affecting design of the preclinical comparability program include but not limited to:**

Quality-related factors:

- Significant differences in the cell expression system of the active substance of the proposed biosimilar compared to that of the reference product.
- Significant differences in purification methods used for both the proposed biosimilar and the reference product.
- The presence of a complex mixture of less well characterized product- and/or process related impurities.

Factors related to pharmaco-toxicological properties of the drug substance:

- Unknown or poorly understood mechanism(s) of action of the drug substance.
- Presence of significant toxicity and/or narrow therapeutic index for the drug substance.
- Limited clinical experience with the reference product.

**B. General considerations:**

- Pre- clinical studies should be comparative in nature between the proposed biosimilar and the reference product.
- More than one aspect of comparability can be addressed in one study depending on the study design (which considers the objective(s), Evaluation criteria, system used...).
- Performing preclinical studies should take into consideration ***"ICH guideline: Note for preclinical safety evaluation of biotechnology-derived pharmaceuticals` (ICH S6)".***

**C. The pre-clinical studies required for evaluating a biosimilar product are:**

**a) In Vitro studies: (Pharmacodynamic Studies):**

Assays like receptor-binding studies or cell-based assays, such data may already be available from quality-related bioassays.



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**b) <u>In Vivo studies: (Pharmacodynamic/Toxicological/ Immunogenicity Studies):</u>**

As a basis to decide to what extent pre-clinical in vivo pharmacodynamic and/or toxicological studies should be part of the comparability exercise, the applicant should consider a risk-based approach which takes into account:

- Specific pharmaco-toxicological properties of the active substance.
- The feasibility and relevance of comparative/non-comparative in vivo testing in a relevant species.

**<u>In vivo studies are performed to address:</u>**

- **Toxicity**
  - At least one repeat dose toxicity study in a relevant species and including toxicokinetic measurements is required to be conducted. Toxicokinetic measurements should include determination of antibody titers, cross reactivity and neutralizing capacity.
  - Selection of species should follow *ICH guideline:preclinical safety evaluation of Biotechnology – derived pharmaceuticals S6(R1) section 3.3*
  - The duration of the study should be based on the intended duration of clinical exposure and disease indication for example:
    - One to three months for most products.
    - Six months duration for products intended for chronic indications although in some cases shorter or longer durations have supported marketing authorizations.
    - Two weeks for products intended for short-term use (*(for example* < 7 days) and for acute life-threatening diseases.

- **Pharmacodynamic effect**
  Activity relevant to clinical indication (can be waived if the available in vitro assays have been validated to reliably reflect the clinically relevant pharmacodynamic activity of the reference product).

- **Local tolerance**
  Evaluated depending on the route of administration, could be part of the repeat dose toxicity study.

- **Immunogenicity**
  Generally animal immunogenicity assessments do not predict potential immunogenic responses to protein products in humans. While antibody measurements, if applicable, should be included in the repeat dose toxicity study to aid in the interpretation of the toxico-kinetic data.



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Generally other routine toxicological studies such as safety pharmacology, reproductive toxicology, genotoxicity and carcinogenicity studies are not required, unless triggered by results of the repeat dose toxicity study or the local tolerance study and/or by other known toxicological properties of the reference product *(for example known adverse effects of the reference product on reproductive function*).

In glycoprotein products, heterogeneity in glycosylation may have a large impact on pharmacokinetics. If this is the case, it may be useful to compare preclinical pharmacokinetics as a part of comparability evaluation for the biosimilar product.

**D. Batches:**

- Preclinical studies should be conducted with the final formulation intended for clinical use, otherwise justification is needed.

## 3- Clinical Aspects:

The scope and extent of clinical studies will depend on the outcomes of the comparability quality and preclinical data.

**A. General Considerations:**

- Clinical studies should be head to head comparative studies betweenthe biosimilar and reference product.
- The clinical comparability exercise is a stepwise procedure that should begin with pharmacokinetic (PK) and pharmacodynamics (PD) studies followed by clinical efficacy and safety trial(s) or, in certain cases, pharmacokinetic/pharmacodynamics (PK/PD) studies for demonstrating clinical comparability.
- More than one aspect of comparability can be addressed in one study depending on the **study design** (which considers the objective(s), evaluation criteria, type of population...).
- Performing clinical studies should follow ICH guidelines taking into consideration the following:

  a) It must be reasonably assured that if a difference between the reference product and biosimilar product exists, then the study is capable of showing that difference.

  b) Route of administration selected (should be the most sensitive route; justification should be submitted).

  c) Type of population included in the study could be healthy or patients but it should be taken into consideration the choice of sensitive population that is able to detect potential differences between the biosimilar and the reference product *(for example, In case of insulin, the study population should consist of non-obese healthy volunteers or patients with type 1 diabetes rather than insulin-resistant obese patients with type 2 diabetes)*.



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**B. Clinical study should address the following aspects:**

a) PK parameters:

- The PK profile is an essential part of the basic description of a medicinal product and should always be investigated.
- PK comparison of the biosimilar and the reference product should not only include absorption/ bioavailability but should also include elimination characteristics; i.e. clearance and/or elimination half-life, since differences in elimination rate of the biosimilar and the reference product may exist.
- Other PK studies such as interaction studies or studies in special population are generally not required.

- Acceptance criteria for the demonstration of similar PK between the Biosimilar product and the Reference product should be pre-defined, justified and clearly documented in the study protocol. (*It is noted that the criteria used for bioequivalence studies were developed for chemically-derived, orally administered products and may not necessarily be applicable for biological medicinal products. Meanwhile, due to the lack of established acceptance criteria designed for biologicals, the traditional 80- 125 % equivalence range is often used. However, if the 90% confidence intervals of the ratio of the population geometric means (test/reference) for the main parameters under consideration (usually rate and extent of absorption) fall outside this traditional range, the biosimilar may still be considered similar to the reference product provided there is sufficient evidence for similarity from the quality, pre-clinical, PD, efficacy and safety comparisons*).
- PK studies should generally be performed for the route(s) of administration applied.
- PK studies should generally be performed using doses within the therapeutic dose range recommended for the reference product.
- The choice of single-dose studies, steady-state studies, or repeated determination of PK parameters and the study population should be justified by the manufacturer *(It should be noted that single dose study is not suitable for measuring immunogenicity)*.
- The ordinary cross-over design may not be appropriate for biological medicinal products with a long half-life or for proteins for which formation of anti-product antibodies is likely.

b) PD markers:

- The pharmacodynamics (PD) markers should be selected on the basis of their relevance to demonstrate therapeutic efficacy of the product. *For example absolute neutrophil count and CD34+ cell count are the relevant PD markers for the activity of granulocyte colony stimulating factor (G-CSF) and could be used in PK/PD studies in healthy volunteers to demonstrate similar efficacy of two G-CSF-containing medicinal products*.



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- Dose determination: using dose/doses within the steep part of the dose-response curve in order to best detect potential differences between the biosimilar and the reference product).
- In many cases, PD parameters are investigated in the context of combined PK/PD studies. Such studies may provide useful information on the relationship between dose/exposure and effect, particularly if performed at different dose levels.

c) Efficacy:

- Clinical efficacy studies should be adequately powered, randomized, and controlled trial(s).
- Studies should preferably be double-blind or at a minimum observer-blind(*In the absence of any blinding, careful justification will be required to prove that the trial results are free from significant bias)*.
- Equivalence designs are preferred for the comparison of efficacy & safety of biosimilar & reference product *In case of using non-inferiority designs justification should be submitted.*
- Equivalence/ non-inferiority margins have to be pre-specified & justified, *i.e. The selected margin should represent the largest difference in efficacy that would not matter in clinical practice.*

d) Safety:

- Pre-licensing safety data should be obtained in a sufficient number of patients to characterize the safety profile of the biosimilar product. Depending on their size and duration, efficacy trials may be sufficient or may need to be extended to provide an adequate safety database.
- Comparison with the reference product should include type, frequency and severity of adverse events/reactions.
- Further close monitoring of clinical safety of the biosimilar is usually necessary in the post-marketing phase.

e) Immunogenicity:

Immunogenicity of biosimilar product should be investigated preauthorization.
Since preauthorization immunogenicity data are often limited, further characterization of the immunogenicity profile may be necessary post-marketing, particularly, if rare antibody-related serious adverse events may occur that are not likely to be detected in the pre-marketing phase.

- The consequences of unwanted immunogenicity may vary considerably, ranging from clinically irreverent to serious & life threatening diseases.



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- Generally, the amount of immunogenicity data obtained from comparative efficacy trial(s) should allow detection of any marked increase in immunogenicity of biosimilar compared to reference product and should be sufficient pre-licensing.
- In case similar efficacy is demonstrated in confirmatory PK/PD study (ies), immunogenicity data in the target population are still needed.
- The required observation period for immunogenicity testing will depend on:
    a. The intended duration of therapy *(In case of chronic administration, one-year data will usually be appropriate pre-licensing to assess antibody incidence & possible clinical implications)*.
    *b.* The expected time of antibody development *( should be justified by the manufacturer).*

**A confirmatory efficacy study is required to demonstrate biosimilarity, this study can be waived if all the following conditions are met:**

- PK of reference product are well characterized and the relationship between dose/response and response/efficacy of the reference product as "concentration – response" curve is known, *(for example. from literature)*
- Structural and functional comparability of biosimilar and reference product can be characterized to a high degree of confidence by physicochemical and in vitro techniques
- The biosimilar product is comparable to the reference product in all preclinical evaluations conducted.
- PK/PD study has demonstrated comparability and has preferentially been done in an inpatient setting with safety measurement (including immunogenicity) for adequate period justified by the applicant and efficacy measurements.
- A comprehensive post marketing risk management plan has been presented that will gather additional safety data with a specific emphasis on gathering immunogenicity data.
- At least one PD marker is accepted as a surrogate marker for efficacy, and the relationship between dose/exposure to the product and this surrogate marker is well known.

If at any step relevant differences between the biosimilar product and the reference product are detected, the reasons need to be explored and justified. If this is not possible, the new product may not qualify as a biosimilar product and a stand-alone application should be considered.

**C. Batches:**

- Clinical studies should be conducted with the final formulation
- As a general rule, it is required to generate the clinical data for the comparability study with the biosimilar product as produced with the final manufacturing process and therefore representing the



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quality profile of the batches to be commercialized. If there was a manufacturing change during development, comparability should be evaluated in line with ICH Q5E Guideline, as necessary.

**D. Extrapolation of indication could be possible if all the following conditions are met:**

a) A sensitive population criterion that is able to detect potential differences between the biosimilar and reference product is used. *(for example, In case of Growth hormone ,treatment-naïve children with GH deficiency usually represent the most appropriate study population as opposed to children with non GH-deficient short stature that are usually less sensitive to the effects of GH. Although adult patients with GH deficiency could also be considered a "sensitive" population, the endpoint used to measure effects of GH treatment (i.e. body composition) is less sensitive than the one used in children (i.e. longitudinal growth) making an equivalence margin more difficult to define.*

b) The clinically relevant mechanism of action and/or involved receptor(s) are the same which addresses but not limited to the following:

- target/receptor(s) for each relevant activity/function of the product
- the binding, dose/concentration response and pattern of molecular signaling upon engagement of target/receptors
- the relationships between product structure and target/receptor interactions
- the location and expression of the target/receptor(s);

c) Safety and immunogenicity of the biosimilar product have been investigated in the patient population that carries the highest risk of an immune response and immune-related adverse events, thus sufficiently characterized and there are no unique/additional safety issues expected for the extrapolated indication(s).

d) The efficacy trial used a non-inferiority study design and demonstrated acceptable safety and efficacy of the biosimilar compared to the reference product, the applicant should provide convincing arguments that this finding can be applied to the extrapolated indications.

**If the above mentioned conditions for extrapolation of efficacy and safety data of the biosimilar to other indication(s) of the reference are not fulfilled, the applicant will need to submit own clinical data to support the desired indication(s).**

*The requirements depend on the existing knowledge about the reference biological medicinal product and the claimed therapeutic indication(s). Available product / disease specific guidelines should be followed when appropriate.*

## VII. Pharmacovigilance

Product pharmacovigilance plan according to the EPVC guidelines should be submitted; this plan should include protocol for post marketing immunogenicity study at the time of submission of the marketing authorization application.



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## VIII. 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

**RMP**: Risk management plan

**SMF:** Site Master File



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## Reference guidelines

- 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-** 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



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