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Draft Guideline for Registration of Biosimilar Products

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Introduction

Regulations for registration of biological products has been recently 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).

This guideline has been developed in order to facilitate the registration of biosimilar products in Egypt through an abbreviated pathway.

I. Background

The difference between the term generic used for description of copies for reference pharmaceutical product and the term biosimilar used to describe the similar versions of reference biological product should be clearly understood.

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 tending to induce an unwanted immune response.

2- Are highly dependent on manufacturing process that affects Product quality, safety & efficacy profile.

Therefore two approaches for registration of a Similar version of a biological product can be applied:

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

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

II. Scope

The scope of this guideline is all biological products intended to be registered as biosimilars to a reference biological product with exception of blood derived products & their recombinant analouges, vaccines and sera.

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III. Definitions

Biological product: 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: Biological product *(other than blood derived products their recombinant analouges, vaccines and sera)* 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 is equivalent to a reference product when prescribed in a claimed indication.

Generic: Copies of chemical, small molecule medicinal products that are structurally and therapeutically equivalent to an originator pharmaceutical product.

Reference Biological product: Product developed and registered on basis of full qualtity, preclinical and clinical dossier and used by the manufacturer of the biosimilar product.

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 batches: Batches of finished product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batches.

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 demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinically acceptable differences.

IV. Registration of a biosimilar product

Two approaches are applied for registration of biosimilar products:

1- **Final dossier approach (for imported products):**

Development process has been already done under supervision of the NRA of manufacturer country of origin and only evaluation of the final product is done.

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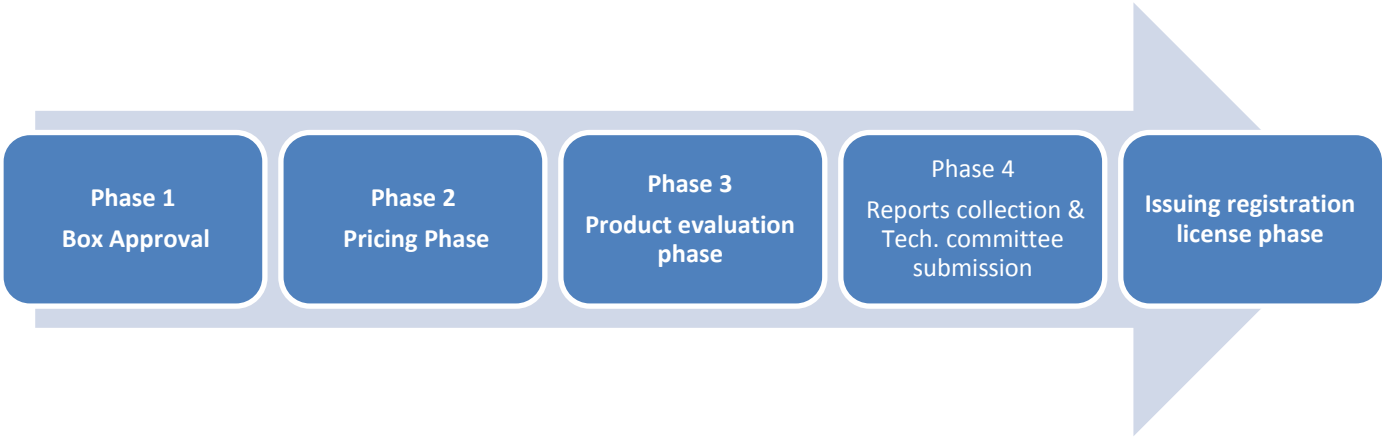


2- Step wise approach (for locally manufactured products):

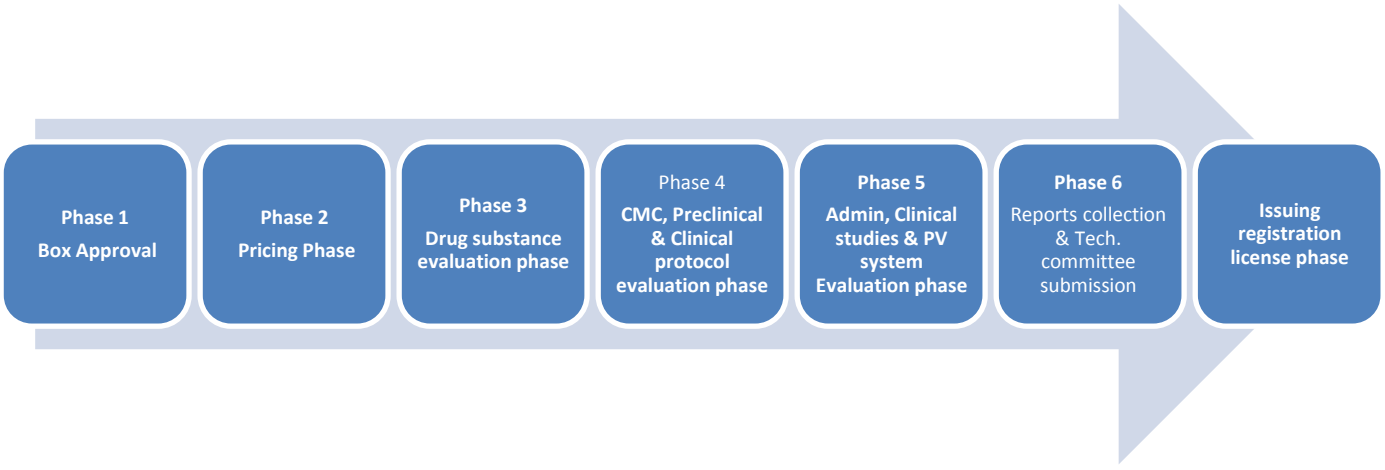
Development and registration processes proceed side by side; the process will be evaluated as phases as follows:

1- Submit the Active substance master file & SMF for evaluation (Evaluation in this stage depends on achieving quality requirements regardless of demonstrating biosimilarity), if approved complete the next steps.

2- Full CMC including stability studies should be performed on suitable number of batches (at least 3 pilot batches and 3 production batches; none of them will be marketed) of the biosimilar product in addition to head to head comparability quality exercise with suitable number of batches of the reference product, if approved complete the next steps .

3- Submit the CMC with the comparability quality data, Preclinical data & clinical protocol for evaluation, if approved complete the next steps.

4- Submit Clinical studies for evaluation.



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V. Principles for Development of Biosimilar products

Development of biosimilar product and the responsibility of 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 submit active substance master file to the authority.

1- Select a reference product:

- A single reference product must be used for all comparability exercises during the development process (i.e. quality, safety and efficacy).
- The reference product should be justified by the manufacturer of the biosimilar product according to the following criteria:
  - 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.
  - Should be either Licensed in Egypt or licensed and widely marketed in a reference country for at least 4 year.
  - 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 manufacturing process of the biosimilar product should employ state-of-the-art science and technology to achieve a high quality biosimilar product that is as similar as possible to the reference product.
- In case of recombinant products, Expression 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.
- Changing the host cell type for development of a biosimilar product could be possible only if the manufacturer can provide a convincing data proving that the structure of the molecule is not affected and that the clinical profile of the product will not change. For example, somatropin produced in yeast cells appears to have similar characteristics to somatropin expressed in E. coli.
- However, the use of a different host cell type will not be feasible for glycoproteins because glycosylation patterns vary significantly between different host cell types. For example, the expression system can have a significant effect on the types and extent of translational and post-translational modifications that are imparted to the proposed protein product.

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- The following guidelines for 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 Q11: Development and manufacture of drug substances–chemical and biotechnological/ biological entities.*

VI. Comparability Key elements

- Complete CMC data should be submitted in CTD format according to ICH guidelines in addition to quality comparability exercise with the reference product
- Head to head preclinical and clinical comparative studies with the same reference product used in the Quality comparability exercise should be submitted. The quantity of the studies required depends mainly on the outcomes of the quality data *(for ex. 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 bio distribution 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):

- Comparability exercise has to be performed on both active substance and drug product level.
- Product characterization studies should be performed using state of the art of the analytical methods on the most intermediate best suited for the analytical procedures used.
- If the finished drug product is best suited for a particular analysis, the characterization should compare the proposed finished biosimilar product and the finished reference product.
- If the finished product is not suitable for characterization methods; comparability exercise may have to be performed on the active substance, the manufacturer may have to extract the drug substance from the reference finished product.

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- Comparative deformulation could be applied for extraction taking into consideration that the applicant should describe the extraction procedure of the drug substance from the reference product and provide support that the extraction procedure itself does not alter product quality. This would include consideration for alteration or loss of the desired products and impurities and relevant product-related substances, and it should include appropriate controls that ensure the relevant product characteristics of the reference product are not significantly altered by the extraction procedure.

Analytical studies carried out to support the approval of a proposed biosimilar product should be part of a broad comparison that includes, but is not limited to, the proposed biosimilar product, the reference product, applicable reference standards, and consideration of relevant publicly available information.

A. Structural characterization and conformation

- 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 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 following the ICH guidelines: Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
- Extensive analytical characterization for different batches of the reference product should be perform, this would enable the applicant to:
  - Detect batch to batch variation within batches of the same reference product.
  - Specify the acceptance criteria for biosimilarity with justification

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- Specifications for the biosimilar product should be set based on the obtained data for the biosimilar and the applicant's own experimental results obtained by testing the reference product
- Specifications should not be wider than the range of variability of the reference product
- Each acceptance criterion should be established and justified based on data obtained from lots used in nonclinical 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 same as analytical methods used for product characterization and for establishing product comparability

This comparability testing regarding specifications includes:

- **Physicochemical properties**

  includes 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)

  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**

  includes but not limited to (Binding assays of the antibody to antigen, Affinity, avidity and immune-reactivity (including cross-reactivity)

- **Purity and impurities**

  Information based on the analysis of samples stored under stress conditions, inducing selective degradation (e.g., oxidation, dimerization) should be used for identification. Comparison of product related substances, and of product-related impurities should be based on specific degradation pathways and potential post-translational modifications of the individual proteins. Accelerated stability studies

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of the reference and of the biosimilar product can be used to further define and compare stability profiles

Impurities is either Process-related or Product-related (process-related impurities do not form part of the comparability exercise; however they must be controlled for as part of biosimilar manufacture) it includes but not limited to Aggregation, Deamidation, Oxidation, Truncation, Charge variants, Visible, sub-visible and sub-sub visible particles

C. Final formulation

- 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
- 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 (e.g., from Ph. Eur., WHO, etc.) should be used for method qualification and validation"

D. Stability

- Complete stability studies for drug substance and drug product following "*ICH guideline Quality of biotechnology products: stability testing of biotechnological/biological products QC5*" should be conducted.
- 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 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 compared with the reference product
- Significant differences in purification methods used
- 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:

- - Mechanism(s) of drug action are unknown or poorly understood
- - The drug substance is associated with significant toxicity and/or has a narrow therapeutic index
- - Limited clinical experience with the reference product

B. General considerations:

- Pre- clinical studies should be head to head comparative studies between the biosimilar and 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 consediration ***"ICH guideline: Note for preclinical safety evaluation of biotechnology-derived pharmaceuticals` (ICH S6)"***

C. The minimum 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/ Toxicologic/ Immunogenicity Studies):</u>

As a basis to decide to what extent non-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>

- **Non clinical toxicity**
  - At least one repeat dose toxicity study in relevant species is required to be conducted.
  - 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.
    - 1-3 months for most products.
    - Two weeks for products intended for short-term use (e.g., < to 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 toxisity 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.

Generally other routine toxicological studies such as safety pharmacology, reproductive toxicology, genotoxicity and carcinogenicity studies are not required, unless triggered by results

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of the repeat dose toxicity study or the local tolerance study and/or by other known toxicological properties of the reference product (*e.g. known adverse effects of the reference product on reproductive function*)

D. Batches:

- Preclinical studies should be conducted with the final formulation
- Types of batches required to conduct preclinical studies are the production batches used in the quality comparability.

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 between the 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) 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).

  d) 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 ex. In case of*

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insulin, the study population should consist of non-obese healthy volunteers or patients with type 1diabetes rather than insulin-resistant obese patients with type 2 diabetes)

B. Clinical study should address the following aspects:

a) PK parameters:

- All (ADME) parameters should be investigated. (*other PK studies such as interaction* s*tudies 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 and clearly documented in the study protocol. (*It is noted that the criteria used 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, non-clinical, PD, efficacy and safety comparisons).*
- PK studies should generally be performed for the routes of administration applied for.
- 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 ex. 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*
- 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.

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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:

(Two studies should be conducted one preauthorization and one post authorization; the preauthorization study should be comparative the post authorization study could be stand-alone)

- The consequences of unwanted immunogenicity may vary considerably, ranging from clinically irreverent to serious & life threatening diseases.
- Generally, the amount of immunogenicity data obtained from comparative efficacy trial(s) will allow detection of a marked increase in immunogenicity of biosimilar compared to reference product & will 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.

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- 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 clinical 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 "concentration – response" curve is known, e.g. 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
- Types of batches required to conduct clinical studies are production scale batches used in the quality and pre-clinical comparability exercise.

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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. e.g. *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).

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

ICH: International Conference on Harmonisation

CAPA: Central Administration for Pharmaceutical Affairs

NORCB: National Organization for Research and Control of Biologics

ASMF: Active substance master file

SMF: Site Master File

CMC: Chemistry, Manufacturing and Control

NRA: National Regulatory authority

EPVC: Egyptian Pharmacovigilance Center

RMP: Risk management plan

PSUR: Periodic Safety Update Report

PK: Pharmacokinetic

ADME: Absorbtion, Distribution, Metabolism, Elimination

PD: Pharmacodynamic

NRA: National Regulatory Authority

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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 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
- **CDSCO**- Indian Biosimilars Guidelines

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