



Guidelines on the Evaluation of Biosimilar Products

Directorate General of Drug Administration
Ministry of Health and Family Welfare
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Message from the Director General, Directorate General of Drug Administration

It is my pleasure that one of the nine functions of DGDA – “Marketing Authorization” *related guidelines are now regularly published from DGDA for different class of drugs.* On this aspect “Guidelines on the evolution of Biosimilar Products” is one of the very important guideline which will help Biotech Industry, Researchers, Academicians as well as Regulators to ensure quality, efficacy and safety of Biosimilar products registered in Bangladesh.

This guideline is prepared harmonizing with EMEA guideline on similar biological medicine, WHO guideline on similar biotherapeutic products (SBPs), Korean guideline on Biosimilar products etc. so that Biosimilar product registration would be given in Bangladesh with a high standard to get global recognition as well as protecting the health of the patients who are in dire need of these products.

I would like to thank the members of working committee for their meticulous job which they performed.

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1. INTRODUCTION

This guidance is intended to assist Importers, manufacturers and others in demonstrating that a proposed therapeutic protein product (proposed product) is biosimilar to a reference product for purposes of the submission of a marketing authorization application under The Drugs Act, 1940, The Drugs Rules, 1945, the Bengal Drug Rules 1946 and The Drugs (Control) Ordinance, 1982.

Biotherapeutic products (biotherapeutics) have a successful record in treating many life-threatening and chronic diseases such as diabetes, autoimmune diseases and cancers. However, their cost has often been high, thereby limiting their accessibility to patients, particularly in developing countries. Recently, the expiry of patents and/or data protection for the first major group of originators' biotherapeutics has ushered in an era of products that are designed to be "similar" to a licensed originator product. A biosimilar is a version of an already registered biotherapeutics that has demonstrable similarity in physicochemical, biological and immunological characteristics, efficacy and safety, based on comprehensive comparability studies. The clinical experience and established safety profile of the originator products should contribute to the development of similar biotherapeutic products. A variety of terms, such as "biosimilar products", "follow-on protein products" and "subsequent-entry biologics" have been coined to describe these products. For the sake of clarity, the term "Biosimilar product" will be used to define such product to be used in the context of Bangladesh. Biosimilars are typically less expensive to produce than the reference medicine, due to lower research and development costs.

The term "generic" medicine is used to describe chemical, small molecule medicinal products that are structurally and therapeutically equivalent to an originator product whose patent and/or data protection period has expired. Demonstration of bioequivalence of the generic medicine to a reference product

is usually appropriate and sufficient proof of therapeutic equivalence between the two. However, the approach established for generic medicines are not suitable for the development, evaluation and licensing of biosimilar products/ since they are relatively large and more complex protein structures that are unlikely to be structurally identical to a reference product. The clinical performance of biotherapeutics can also be much influenced by the manufacturing process and some clinical studies will be required to support the safety and efficacy of a biosimilar product. In addition, it is important to note that a biosimilar product that is not shown to be similar to the original product should not be described as "similar".

Therefore, a comparability evaluation is required for the sake of quality, safety, and efficacy for public health purposes. In this context, regulatory bodies like EMA, USFDA and others have issued regulatory guidelines on biosimilar products. In order to evaluate biosimilar products and review authorization of biosimilar products for marketing in Bangladesh, comments and suggestions from experts in this field have been invited and various documents issued by overseas governments and/or WHO have been reviewed to generate this document.

2. SCOPE

This guideline addresses the general principles for the Quality, Non-clinical and Clinical development and assessment of the marketing authorization applications of biosimilar product. In principle, this document can apply to all types of biosimilar products. However, in this case, it applies specifically to biosimilar products that contain well-characterized protein as the active ingredient and of which comparability can be demonstrated through characterization, non-clinical studies, and clinical studies. Nevertheless, the principles explained here could apply to other biosimilar products, on a case by case basis.

3. GENERAL CONSIDERATIONS

A biosimilar product is usually developed in the sequential process of carrying out some non-clinical studies and clinical studies to demonstrate the comparability of the biosimilar product to the reference product already authorized for manufacture, marketing, or import, on condition that the quality of the biosimilar product is comparable to the reference product.

Like other biological products, a biosimilar product is evaluated in terms of quality, safety, and efficacy. When compared to a new drug, it is expected that less information is submitted to get product authorization. However, this practice is acceptable only if the comparable quality of the biosimilar product is demonstrated through extensive quality evaluations. Depending on the nature of the reference product already authorized, the degree and extent of such evaluation activities may vary.

For the biosimilar product, extrapolation of the reference product's indications is the major characteristic compared to other biological products. Even if all clinical studies are not performed for all indications of the reference product, it is possible to apply all clinical indications authorized for the reference product on condition that comparability is assured.

This document describes how to evaluate the comparability of a biosimilar product to a reference product through quality, safety, and efficacy studies.

4. DEFINITIONS

The definitions given below apply to the terms used in this document.

- 4.1 **Biological Product or Biologic:** A “biological product, or biologic”, is a preparation, such as a drug or a vaccine, that is made from living organisms. Compared with conventional chemical drugs, biologics are relatively large and

complex molecules. They may be composed of proteins (and/or their constituent amino acids), carbohydrates (such as sugars), nucleic acids (such as DNA or RNA or modified RNA), or combinations of the substances. Biologics may also be cells or tissues used in transplantation.

4.2 Biosimilar Product: A "biosimilar product" is a biological product that is comparable to already marketed reference products in terms of quality, safety and efficacy.

4.3 Reference Product: A "reference product" is a drug product already authorized by a regulatory authority on the basis of full regulatory submissions. The reference product is used in demonstrating the comparability of a biosimilar product through quality, non-clinical studies and clinical studies.

4.4 Originator Product: An "originator product" is a drug product firstly authorized by a regulatory authority on the basis of full regulatory submissions. In general, a drug product with safety data publicly available and long-term marketing experience may be used as a reference product.

4.5 Comparability: "Comparability" is a scientific comparison of a biosimilar product with a reference product with the goal to establish that no detectable difference exists in terms of quality, safety, and efficacy.

4.6 Equivalence: "Equivalence" is the state of being equal or virtually identical in major clinical endpoints of interest. In addition, any observed differences are of no clinical relevance.

4.7 Immunogenicity: "Immunogenicity" is the ability of a substance to trigger an immune response or reaction, such as development of specific antibodies, T-cell response, allergic or anaphylactic reaction.

4.8 Active Pharmaceutical Ingredient (API): "API" is any substance or mixture

of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

4.9 Drug Substance: “Drug substance” is the active pharmaceutical ingredient and associated molecules that may be subsequently formulated, with excipients, to produce the drug product.

4.10 Drug Product: “Drug product” is a pharmaceutical product type in a defined container closure system that contains a drug substance, generally in association with excipients.

4.11 Excipient: “Excipient” is an ingredient added intentionally to the drug substance which should not have pharmacological properties in the quantity used.

4.12 Cell Culture: “Cell culture” is the process by which cells that are no longer organized into tissues are grown in vitro under defined and controlled conditions. Cell cultures are operated and processed under axenic conditions to ensure a pure culture absent of microbial contamination.

4.13 Cell Line: “Cell line” is type of cell population which originates by serial subculture of a primary cell population, which can be banked.

4.14 Cell Bank: “Cell bank” is a collection of appropriate containers, whose contents are of uniform composition, stored under defined conditions. Each container represents an aliquot of a single pool of cells.

4.15 Master Cell Bank (MCB): “MCB” is an aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined

conditions, dispensed into multiple containers and stored under defined conditions. The MCB is used to derive all working cell banks. The testing performed on a new MCB (from a previous initial cell clone, MCB or WCB) should be the same as for the MCB unless justified.

4.16 **Working Cell Bank (WCB):** “WCB” is the Working Cell Bank is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the MCB under defined culture conditions.

4.17 **Contamination:** “Contamination” is the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

4.18 **Cross-contamination:** “Cross-Contamination” is contamination of a material or product with another material or product.

4.19 **Bioburden:** “Bioburden” is the level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

4.20 **Virus:** “Virus” is intracellular replicating infectious agents that are potentially pathogenic, possessing only a single type of nucleic acid (either RNA or DNA), is unable to grow and undergo binary fission, and multiply in the form of their genetic material.

4.21 **Viral Clearance:** “Viral clearance” is elimination of target virus by removal of viral particles or inactivation of viral infectivity.

4.22 **Virus Inactivation:** “Virus inactivation” is reduction of virus infectivity caused by chemical or physical modification.

- 4.23 **Virus Removal:** “Virus removal” is physical separation of virus particles from the intended product.
- 4.24 **Expression Construct:** “Expression construct” is the expression vector which contains the coding sequence of the recombinant protein and the elements necessary for its expression.
- 4.25 **Comparability Bridging Study:** “Comparability bridging study” is a study performed to provide nonclinical or clinical data that allows extrapolation of the existing data from the drug product produced by the current process to the drug product from the changed process.
- 4.26 **Comparable:** “Comparable” is a conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion.
- 4.27 **Comparability Exercise:** “Comparability exercise” is the activities, including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable.
- 4.28 **Quality:** “Quality” is the degree to which a set of inherent properties of a product, system or process fulfills requirements.
- 4.29 **Quality Risk Management (QRM):** “QRM” is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.
- 4.30 **Quality System:** “Quality System” is the sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

- 4.31 **Product Lifecycle:** “Product lifecycle” is all phases in the life of the product from the initial development through marketing until the product’s discontinuation.
- 4.32 **Quality Attribute:** “Quality attribute” is a molecular or product characteristic that is selected for its ability to help indicate the quality of the product. Collectively, the quality attributes define identity, purity, potency and stability of the product, and safety with respect to adventitious agents. Specifications measure a selected subset of the quality attributes.
- 4.33 **Biological Activity:** “Biological activity” The specific ability or capacity of the product to achieve a defined biological effect. Potency is the quantitative measure of the biological activity.
- 4.34 **Contaminants:** “Contaminants” are any adventitiously introduced materials (e.g., chemical, biochemical, or microbial species) not intended to be part of the manufacturing process of the drug substance or drug product.
- 4.35 **Impurity:** "Impurity" is any component present in the drug substance or drug product which is not the desired product, a product-related substance, or excipient including buffer components. It may be either process- or product-related.
- 4.36 **Process-related Impurities:** “Process-related impurities” are impurities that are derived from the manufacturing process. They may be derived from cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or downstream processing (e.g., processing reagents or column leachable).
- 4.37 **Product-related Impurities:** “Product-related impurities” are molecular variants of the desired product (e.g., precursors, certain degradation products

arising during manufacture and/or storage) which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety.

4.38 Product-related Substances: “Product-related Substances” are molecular variants of the desired product formed during manufacture and/or storage which are active and have no deleterious effect on the safety and efficacy of the drug product. These variants possess properties comparable to the desired product and are not considered impurities.

4.39 Reference Standards: “Reference standards” are referring to international or national standards.

4.40 Specification: “Specification” is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. “Conformance to specification” means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

4.41 Validation: “Validation” is a documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce result meeting pre-determined acceptance criteria.

4.42 Analytical Procedure: “Analytical procedure” is the analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations,

use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.

4.43 Conjugated Product: “Conjugated product” is made up of an active ingredient (for example, peptide, carbohydrate) bound covalently or non-covalently to a carrier (for example, protein, peptide, inorganic mineral) with the objective of improving the efficacy or stability of the product.

4.44 Degradation Product: “Degradation Product” is a molecule resulting from a change in the drug substance (bulk material) brought about over time. For the purpose of stability testing of the products described in this guideline, such changes could occur as a result of processing or storage (e.g., by deamidation, oxidation, aggregation, proteolysis). For biotechnological/biological products some degradation products may be active.

5. SELECTION OF REFERENCE PRODUCT

The reference product selected for development of a biosimilar product should be an originator’s biological product authorized in Bangladesh. However, if a reference product authorized in Bangladesh is not commercially available or if there are other justifiable reasons, the same biological product as the one authorized in Bangladesh may be purchased from overseas markets and used as the reference product in the development of the biosimilar product.

The same reference product should be used throughout the quality, safety and efficacy comparability program during the development of a biosimilar product. The dosage form, dose, and route of administration of the biosimilar biological product should be identical to those of the reference product.

There should be sufficient accumulated data on the safety and efficacy of the reference product. In special cases, where it is difficult to determine which product is the originator (for example Human Insulin) or where the originator

product is not commercially available anywhere, the applicant should consult with DGDA and DGDA will advise on best available option to choose as reference product. In case of any ambiguity, DGDA decision will be considered as final.

6. QUALITY EVALUATION

The manufacture of biological drug substances and drug products involves biological processes and materials, such as cultivation of cells or extraction from living organisms. As these biological processes may display inherent variability, the range and nature of by-products may also be variable. As a result, quality risk management (ICH Q9) principles are particularly important for this class of materials and should be used to develop the control strategy across all stages of manufacture so as to minimize variability and reduce the opportunity for contamination and cross-contamination. So, these principles should be used to develop the control strategy across all manufacturing and control stages across the opportunity storage, personnel and materials flow, manufacture and packaging, quality control, quality assurance, storage and distribution activities.

Biological products, like any pharmaceutical product, should be manufactured in accordance with the requirements of a pharmaceutical quality system (ICH Q10) based on a life-cycle approach (ICH Q12). Due to the inherent variability of biological processes and starting materials, ongoing trend analysis and periodic review are particularly important elements of pharmaceutical quality system. Thus, special attention should be paid to starting material controls, change control, trend analysis and deviation management in order to ensure production consistency. Monitoring systems should be designed so as to provide early detection of any unwanted or unanticipated factors that may affect the quality, safety and efficacy of the product. The effectiveness of the control strategy in monitoring, reducing and managing such risks should be regularly reviewed and the systems updated as required taking into account scientific and technical progress.

6.1 Current Good Manufacturing Practice (cGMP) of the manufacturing facility:

The manufacture, control and administration of biological active substances and finished products require certain specific considerations and precautions arising from the nature of these products and their processes. Unlike conventional pharmaceutical products which are manufactured using chemical and physical techniques capable of a high degree of consistency, the manufacture of biological active substances and finished products involves biological processes and materials, such as cultivation of cells or extraction from living organisms. As these biological processes may display inherent variability, the range and nature of by-products may also be variable. As a result, quality risk management (QRM) principles are particularly important for this class of materials and should be used to develop the control strategy across all stages of manufacture so as to minimize variability and reduce the opportunity for contamination and cross-contamination.

All analytical methods used in the quality control and in-process control of biological products should be well characterized, validated and documented to a satisfactory standard in order to yield reliable results. The fundamental parameters of this validation include linearity, accuracy, precision, selectivity/specificity, sensitivity and reproducibility.

For test methods described in relevant pharmacopoeial monographs, qualification of the laboratory test equipment and personnel should be performed. In addition, repeat precision and comparability precision should be shown in the case of animal tests. Repeatability and reproducibility should also be demonstrated by reviewing retrospective test data.

Example of some Orthogonal Methods of Analysis Used with Biopharmaceutical Products:

METHOD	ATTRIBUTES
pH	Solution hydrogen ion, stability
Karl Fisher (lyophilized)	Moisture, stability
Appearance (liquid, lyophilized)	Physical quality, stability
Light Obscuration, MFI	Subvisible Particles, Leachates
UV Absorbance	Concentration
SDS-PAGE (R/NR)	Identity, purity, stability (aggregation, hydrolysis)
SEC-HPLC/UPLC	Identity, purity, stability (aggregation, hydrolysis)
RP-HPLC, HIC-HPLC/UPLC	Identity, stability (deamidation, oxidation, etc.)
Peptide Mapping	Identity, stability (deamidation, oxidation, DS, etc.)
IEF, CIEF, ICE, IEX-HPLC/UPLC	Identity, stability (hydrolysis, desialylation)
CE-SDS (R/NR)	Identity, stability (aggregation, hydrolysis)
Immunoassay, ECL	Process Residuals (proteins)
qPCR	Process Residuals (nucleic acids)
Ligand binding Assay	Bio-Identity, potency, stability
Cell-Based Bioassay	Bio-Identity, potency, stability
N terminal Sequencing	Identity, heterogeneity
C- terminal Sequencing	Identity, heterogeneity
Amino Acid Analysis	Identity, composition, concentration
Monosaccharaides (HPAE-PAD)	Identity, composition
Sialic Acid	Identity, composition, stability (desialylation)
Mass Spectrometry	Identity, purity, stability (oxidation, hydrolysis, DS)
Circular Dichroism	Conformation
FTIR	Conformation
AUC /HPLC /SEC	Impurities (Aggregates)

The GMP inspection should be carried out based on principles mentioned in WHO Technical Report Series No. 996, 2016, Annex 3: WHO good manufacturing practices for biological products

6.2 Manufacturing process

Since a biosimilar product is produced according to its own specific manufacturing process, a complete description of the manufacturing process for the drug substance and drug product should be provided in detail. The manufacturing process should be reasonable and justifiable taking into account the modern science and technology and the nature of the drug product. In addition, it should be demonstrated that the manufacturing process is able to consistently produce the biosimilar product meeting the quality requirements in compliance with the GMP requirements. Submissions should include the information on quality control/quality assurance, in-process controls, and concurrent process validation.

In addition, if a change is introduced to the manufacturing process of the biosimilar product, the comparability studies as described in the "Guidelines on Evaluation of Changes to Manufacturing Processes for Biological Products" or ICH Q5E guideline should be carried out and the comparability of the biosimilar products manufactured before and after such change should be evaluated.

6.3 Comparability studies for quality evaluation

Quality comparison of a biosimilar product and a reference product is a fundamental element in a comparability study. Quality aspects should always be appropriately studied and evaluated with regard to any implications for safety and efficacy. Information on characterization studies, including a comparability study versus a reference product, should be provided. Representative batches produced according to a manufacturing process with proven consistency should be used in

comparability studies.

The purpose of these comparability studies is to demonstrate that a biosimilar product is comparable to a reference product in terms of quality, safety, and efficacy. Therefore, the drug substance (active ingredient) and the drug product should be evaluated in comparability studies and the comparability should be finally determined under comprehensive consideration of quality, non-clinical and clinical data. It is not expected that the quality attributes of the biosimilar product and the reference product will be identical. In such instances, supportive information demonstrating that such differences will not affect the safety and efficacy should be provided.

State-of-the-art analytical techniques and validated analytical procedures which are able to detect any differences between a biosimilar product and a reference product are recommended in a comparability study.

If it is intended to isolate an active ingredient from a reference product because direct comparison at the drug substance level is difficult, supportive information demonstrating that the sample preparation is suitable and the characteristics of the isolated active ingredient are not changed should be provided.

Major process attributes that may affect the product characteristics, adequacy of process controls, and the need for additional non-clinical and clinical data should be considered.

6.3.1 Characterization

Extensive state-of-the-art characterization studies should be performed to demonstrate that the quality of the biosimilar product is comparable to the reference product. Characterization studies should at least include the

physicochemical properties, biological properties, immunological properties, purity (process-related and product-related impurities), contaminants, potency, and strength. (Characterization studies may be performed in accordance with the "Guidelines on Specifications of Biotechnological/ Biological Products" or the ICH Q6B guideline.) Characterization studies should be designed to allow direct comparison of the biosimilar product and the reference product at drug product levels. However, if characterization studies result in different patterns, the implications of such differences should be evaluated and additional characterization studies may be required.

6.3.2 Structural/physicochemical properties

The physicochemical characterization should include the determination of composition, physicochemical properties, and primary and higher order structures of the active ingredient of the biosimilar product. If the appropriate higher order structural information cannot be obtained, a relevant biological activity assay may indicate a correct conformational structure. In such instances, the analytical procedures for determination of biological activity should have appropriate precision and accuracy. In addition, if process-related and product-related impurities are generated or if degradation products are identified through stress and accelerated stability studies, such impurities and/or degradation products should also be evaluated.

An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic process. Therefore, the biosimilar product may contain a mixture of post-translationally modified forms. Appropriate efforts should be made to investigate and identify such forms.

6.3.3 Biological properties

Since proteins used as biological products have a wide range of biological properties, various biological assays should be considered in determining the biological activity. Biological assays can be used in determining the action mechanism of the relevant protein and, in some cases, be linked to clinical activity. Therefore, a set of relevant functional assays designed to evaluate the range of activities of a product with multiple biological activities should be developed and employed.

The biological activity assay is a method to determine the function of a protein and, if there are changes to the quality of a drug product, it can be used to verify if such changes are caused by either a product-related substance with biological activity or an impurity without biological activity. In addition, the biological activity assay can be used in verifying the protein's higher order structure. Therefore, the biological assay can also serve as a complement to physicochemical analysis. If a biological assay with appropriate accuracy and precision is used, it is possible to demonstrate that a biosimilar product is not significantly different from a reference product in terms of biological functions. However, since the biological activity assay usually has considerable variability, it should be considered that the biological assay may not be able to detect any differences from the reference product.

The results of the biological assay should be provided and expressed in units of activity calibrated against an international or national reference standard, when available and appropriate. Such assays should comply with appropriate compendial requirements for biological assays, if applicable.

6.3.4 Immunological properties

Since the presence of any product- or process-related impurities or post-transnationally modified forms may trigger immunological responses, it is important to characterize the immunological properties of a biosimilar product. If immunological properties are part of the characterization studies (e.g., for antibodies or antibody-based products), the specificity, affinity, binding activity, Fc function, and others of the biosimilar product should be evaluated in comparison with those of the reference product. In addition, the results from the immunogenicity studies in animal models should be considered.

6.3.5 Purity (impurities)

The purity and impurity profiles of the drug substance and the drug product should be assessed both qualitatively and quantitatively by a combination of analytical procedures. Accelerated conditions, other conditions that may cause degradation, and potential post-translational modifications should be considered in evaluating the impurity profiles.

The product-related impurities in the biosimilar product should be identified and compared to the reference product using the state-of-the-art technologies. If possible, application of more than one analytical technology to each should be considered.

Since the biosimilar product is produced according to its own unique manufacturing process different from that for the reference product, the process-related impurities in the biosimilar product may be quantitatively and qualitatively different from those in the reference product. Therefore, although the quantitative comparison may not be relevant in the comparability study, the state-of-the-art analytical technologies should be applied to verify the impact of these

process-related impurities.

In-process acceptance criteria and action limits for impurities should be appropriately established to assure the quality of the drug substance and the drug product. Any new impurities should be evaluated in terms of quality, safety, and efficacy.

6.4 Specifications

Specifications should be established for routine quality controls. Product-specific tests to be included in the specifications should be selected to assure the quality of the biosimilar product and should comply with the requirements as specified in the relevant regulations or guidelines.

If a pharmacopoeial monograph such as USP, BP, JP or International pharmacopoeia is available for the biosimilar substance or finished product then the specification should be based on pharmacopoeia. In cases there is no pharmacopoeial monograph available, the specification should be based on ICH Q6B. For reference purpose, Critical Quality Attributes (CQA) / test specification of different types of biosimilar products are given at Annexure 4, which should be taken into consideration.

Each acceptance criterion should be established and justified based on data obtained from representative lots (such as data obtained from lots used in non-clinical and/or clinical studies, data from lots used for the demonstration of manufacturing consistency, data from stability studies, relevant development data, and data obtained from the comparability studies (quality, safety, and efficacy) and justifications for the methods used and the proposed range should be provided.

6.5 Analytical procedures

In order to demonstrate that the quality of the biosimilar product is comparable to the reference product, extensive state-of-the-art characterization studies should be applied at both the drug substance (active ingredient) and the drug product levels.

Given the complexity of the protein and its inherent heterogeneity, more than one analytical technology may be required for each quality attribute, in order to sufficiently characterize the physicochemical and biological properties.

Although validated analytical procedures are not necessarily required, analytical procedures used in the characterization studies should be scientifically sound and be able to produce reliable results. Analytical procedures included in the specifications should be appropriately validated.

6.6 Stability studies

Long-term stability study should be carried out in order to establish the shelf-life (expiry) period and storage conditions of the drug product. Although a comparative stability study (with the reference product) is not necessarily required, accelerated and stress stability studies to establish the impurity profiles at drug substance and drug product levels are often useful in determining the comparability of the biosimilar product and the reference product. The stability studies should be performed on the basis of the representative conditions, including the container-closure system. The stability studies may be designed and performed in accordance with the "Guidelines on Stability Study of Biological Products" and the ICH Q5C guideline.

7. NON-CLINICAL EVALUATION

In order to establish the safety and efficacy of a biosimilar product, non-clinical and clinical evaluations are usually required, in addition to comprehensive quality evaluation.

In principle, non-clinical studies should be conducted with the final formulation intended for clinical use. However, if it is not possible to perform non-clinical studies with such final formulation (toxicity studies requiring administration of high dose), minimal modifications may be made within the justifiable range so as to allow the performance of non-clinical studies. In addition, the dosage form, dose, and route of administration of a biosimilar product should be identical to those of a reference product. Any differences in dosage form, dose, and route of administration should be justified.

Since non-clinical studies of a biosimilar product are conducted as a part of the comparability, they should be designed to demonstrate the comparability of the biosimilar product through comparative studies with a reference product. Such non-clinical studies may be conducted in accordance with existing relevant guidelines (such as ICH S6 document). Design of an appropriate non-clinical study requires a clear understanding of the product characteristics. Results from characterization should be reviewed from the point-of-view of potential impacts on efficacy and safety.

The same reference product should be used throughout non-clinical studies and it should be the one used in quality and efficacy evaluations.

The following in vivo and in vitro studies may be considered and should be tailored to the specific product concerned on a case-by-case basis. The approach taken will need to be fully justified.

7.1 *In vitro* studies

Assays, such as receptor-binding studies or cell-based assays (cell-proliferation), should normally be undertaken in order to establish the comparability of the biological/ pharmacodynamics activity of the biosimilar product and the reference product. Such data are usually already available from the biological assays of the quality evaluation. These studies may be referenced in the non-clinical evaluation.

7.2 *In vivo* studies

Animal studies should be performed in species known to be relevant, designed to maximize the information obtained (e.g., a species in which the reference product has shown to possess pharmacodynamics and/or toxicological activity), and employ state-of-the-art technology. In general, consideration should be given to the following conclusions:

7.2.1 Biological / pharmacodynamics activity relevant to the clinical application:

These data should usually be available from biological assays described in the quality evaluation and these studies can be made in the non-clinical part of the dossier, if feasible.

7.2.2 Non-clinical toxicity as determined in at least one repeat dose toxicity study in a relevant species and including toxicokinetics measurements:

If possible, these measurements should include determination and characterization of antibody responses. The duration of the studies should be sufficiently long to allow detection of potential differences in toxicity and antibody responses between the biosimilar product and the reference product. Although the predictive value of animal models for immunogenicity in humans is considered

low, data from immunogenicity studies in animal models are useful in interpretation of toxicokinetics data and assessment of overall comparability studies.

In addition, the comparative repeat dose toxicity study is useful in predicting any “unexpected” toxicity during clinical use of the biosimilar product. If performed with the final formulation intended for clinical use, the repeat dose toxicity study will, in principle, allow for detection of potential toxicity associated with the active ingredient and product and process-related impurities.

7.2.3 Local tolerance study:

Depending on the route of administration of a biosimilar product, the local tolerance study may be performed. If appropriate, the evaluation can be performed by a part of repeat dose toxicity study.

7.2.4 Other toxicological studies:

If the comparability of the biosimilar product and the reference product is verified through quality evaluation, other toxicological studies, such as safety pharmacology, reproductive toxicology, genotoxicity, and carcinogenicity studies, are not generally required, unless triggered by results of the repeat dose toxicity study and/or by other known toxicological properties of the reference product (e.g., known adverse effects of the reference product on reproductive function).

8. CLINICAL EVALUATION

Pivotal clinical data should be generated using the product derived from the final manufacturing process. If the manufacturing process of the drug products used in clinical studies is different from the final manufacturing process for which marketing authorization is sought, such differences should be justified and additional data may be required.

The clinical comparability studies include pharmacokinetic, pharmacodynamics, and efficacy studies. If the comparability can be demonstrated by confirmatory pharmacokinetic / pharmacodynamics data, an efficacy study may be omitted.

8.1 Pharmacokinetic (PK) studies

The PK profile is an essential part of the basic description of a drug product and should always be investigated. PK studies should generally be performed for all proposed routes of administration and using doses within the therapeutic dose range recommended for the reference product.

PK studies should be comparative in nature to demonstrate the comparability of the biosimilar product and should be designed to enable detection of potential differences between the biosimilar product and the selected reference product. This is usually best achieved by performing single-dose PK studies in a sensitive and homogenous study population and by using a dose where the sensitivity to detect differences is largest. For example, for a drug product with saturable absorption (saturation kinetics), the lowest therapeutic dose would be most appropriate, provided that the employed assay can measure the resultant drug plasma levels with sufficient accuracy and precision. Comparative PK studies could be performed in healthy volunteers as a sufficiently sensitive and homogenous population, if considered ethical.

The choice of single-dose studies, steady-state studies, or repeated determination of PK parameters and the study population should be justified. The cross-over design may not be appropriate for biological products with a long half-life or for proteins for which formation of anti-product antibodies is likely. Therefore, if the cross-over design is adopted, it is necessary to demonstrate that the half-life, antibody formation, and other characteristics do not affect the PK profiles. If the parallel design is selected, careful attention should be paid to avoid potential

imbalances between groups.

Since differences in elimination rate of the biosimilar product and the reference product may exist, the PK comparison should include absorption/bioavailability as well as elimination characteristics, i.e., clearance and/or elimination half-life.

Acceptance criteria for demonstration of similar PK between the biosimilar product and the reference product should be pre-defined and appropriately justified. The criteria used in standard clinical PK comparability studies (bioequivalence studies) developed for chemically-derived, orally administered products may not be applicable for biological products.

If there is evidence of comparability from the quality and non-clinical studies, other PK studies, such as interaction studies (with drugs likely to be used concomitantly) or studies in special populations (e.g., children, the elderly and patients with renal or hepatic insufficiency) are not usually required for a biosimilar product.

Historically, the PK evaluation of peptide or protein products has suffered from limitations in the assay methodology, thus limiting the usefulness of such studies. Special emphasis should therefore be given to the analytical method selected and its capability to detect and follow the time course of the protein (the parent molecule and/or metabolites). The method should be optimized to have satisfactory specificity, sensitivity and a range of quantification with adequate accuracy and precision.

If the active ingredient of a biosimilar product is an endogenous protein and the concentration of the endogenous protein is measurable, the concentration-time profile of the administered exogenous protein may be substantially affected. In such cases, the approach to minimize the influence of the endogenous protein on the results should be described and justified.

8.2 Pharmacodynamics (PD) studies

In general, the pharmacodynamics (PD) studies may be performed in combination with PK studies and the PD parameters should be selected on the basis of their relevance to demonstrate clinical efficacy. Since biological products may have different PK and dose-response relationships, combined PK/PD studies may provide useful information in evaluating the comparability of the biosimilar product and the reference product. Such studies may provide useful information on the relationship between dose/exposure and effect, particularly if performed at different doses.

In the comparative PD studies, PD effects should be investigated in a suitable patient population using one dose within the steep part of the dose-response curve in order to best detect potential differences between the biosimilar product and the reference product. If it is possible to use PD markers well established in healthy volunteers, the comparative evaluation of PD effects may be conducted using healthy volunteers.

Usually, the clinical comparability of the biosimilar product and the reference product should be demonstrated in the efficacy studies. However, if similar PD profiles are obtained, the equivalence in efficacy trials can be expected.

8.3 Confirmatory PK/PD studies

Usually, clinical trials are required to demonstrate similar efficacy between the biosimilar product and the reference product. However, comparative PK/PD studies may be appropriate for the following cases and additional efficacy study is not required in following cases:

- a. If the PK and PD properties of the reference product are well-characterized.

- b. If at least one PD marker is an accepted surrogate-marker for efficacy.
- c. If the relationship between dose/exposure, the relevant PD marker(s), and response/efficacy of the reference product is well-established.

The study population and dosage should represent a test system known to be sensitive to detect potential differences between the biosimilar product and the reference product. Otherwise, it will be necessary to investigate a relevant dose range to demonstrate that the test system is discriminatory. In addition, the acceptance ranges for demonstration of comparability in confirmatory PK and PD parameters should be pre-defined and appropriately justified.

8.4 Efficacy studies

Dose finding studies are not required for biosimilar products, since the dosage and administration of the reference product are usually adopted.

If the dosage and administration of a reference product are adopted for a biosimilar product and if it is intended to extrapolate efficacy data to other approved indications of the reference product (including extrapolation to other dosage, equivalence design is more desirable than non-inferiority design. Equivalence margin should be pre-defined and appropriately justified. In other words, the margin should be selected within the range that would not show any clinical differences from the reference product.

Similar efficacy of the biosimilar product and the reference product should be demonstrated in an adequately powered, randomized, and parallel group clinical trial ('equivalence trials'). Such clinical studies should preferably be double-blinded or at a minimum observer-blinded. In the absence of any blinding, careful justification is required to prove that trial results are free from significant bias.

Potential differences between the biosimilar product and the reference product should be investigated in a sensitive and preferably well-established model. For

example, in the case of hormone, patients with hormone deficiency may be the most appropriate study population.

8.5 Safety

Pre-authorization safety data should be obtained in a sufficient number of patients to characterize the safety profile of the biosimilar product.

In general, safety data obtained from clinical trials may be about frequent and short-term adverse reactions. Comparison with the reference product should include type, frequency and severity of adverse reactions. Such safety data obtained from clinical trials are usually sufficient for product authorization, but further close monitoring of clinical safety of the biosimilar product is usually necessary in the post-marketing phase.

8.6 Immunogenicity

The immune response against a biological product is influenced by many factors such as the nature of the active ingredient, impurities, excipients, stability of the product, route of administration, dosage, and patient- and disease-related factors. The consequences of unwanted immunogenicity may vary considerably, ranging from clinically irrelevant to serious and life-threatening. For example, the formation of neutralizing antibodies alters the pharmacodynamics effects, binding antibodies often affect pharmacokinetics, and the anti-product antibody formation might significantly affect the safety. Accordingly, the frequency and type of antibodies induced as well as possible clinical consequences of the immune response may need to be compared for a biosimilar product.

8.7 Extrapolation to other clinical indications

If similar efficacy and safety of the biosimilar product and the reference product have been demonstrated for a particular clinical indication, extrapolation of these data to other indications of the reference product for clinical which post-marketing survey was completed may be possible if all of the following conditions are fulfilled:

- a. A sensitive clinical test model has been used that is able to detect potential differences between the biosimilar product and the reference product.
- b. The clinically relevant mechanisms of action and/or involved receptor(s) are the same.
- c. Safety and immunogenicity have been sufficiently characterized.

9. PHARMACOVIGILANCE

As for most biological medicines, data from pre-authorization studies are usually too limited to identify all potential unwanted effects of a biosimilar product. In particular, rare adverse events are unlikely to be encountered in the limited clinical trial populations being tested with the biosimilar product. Further close monitoring of the clinical safety of a biosimilar product in all approved indications and a continued benefit-risk assessment are therefore necessary in the post-marketing phase.

The manufacturer should submit a safety specification and pharmacovigilance plan at the time of submission of the marketing authorization application. The principles of pharmacovigilance planning can be found in relevant guidelines such as ICH E2E. The safety specification should describe important identified or potential safety issues for the reference product and for the substance class and/or any that are specific for the biosimilar product. The pharmacovigilance plan should describe the planned post-marketing activities and methods based on the safety specification. In some cases, risk minimization measures such as

educational material for patients and/or treating physicians may enhance the safety of using the biosimilar product. Post marketing observational study report on reasonable subjects shall have to be submitted to DGDA.

Any specific safety monitoring imposed on the reference product or product class should be incorporated into the pharmacovigilance plan for the biosimilar product, unless a compelling justification can be provided to show that this is not necessary. Moreover, potential additional risks identified during the review of the data obtained with the biosimilar product should be subject to further safety monitoring (e.g. increased immunogenicity that might result from a difference in the glycosylation profile).

Post-marketing safety reports should include all information on product tolerability received by the marketing authorization holder. The safety information must be evaluated in a scientific manner and should include evaluation of the frequency and causality of adverse events.

Manufacturers should ensure that, at the time of the marketing authorization, they have in place an appropriate pharmacovigilance system, including the services of a qualified person responsible for monitoring pharmacovigilance and the necessary means for notification of adverse reactions that occur in any of the countries where the product is marketed.

After the marketing authorization is granted, it is the responsibility of the DGDA to monitor closely the compliance of manufacturers with their marketing commitments, where appropriate, and particularly with their pharmacovigilance obligations (as previously described).

10. PRESCRIBING INFORMATION AND LABEL

The biosimilar product should be clearly identifiable by a unique brand name. Where an INN is defined, this should also be stated; WHO policy on INN should be followed

(<http://www.who.int/medicines/services/inn/innquidance/en/index.html>).

The prescribing information for the biosimilar product should be as similar as possible to that of the reference product except for product-specific aspects, such as different excipient(s). This is particularly important for posology and safety-related information, including contraindications, warnings and adverse events. However, if there are fewer indications for the biosimilar product than for the reference product, the related text in various sections may be omitted unless it is considered important to inform doctors and patients about certain risks, e.g. as a result of potential off-label use. In such cases it should be clearly stated in the prescribing information that the biosimilar product is not intended for use in the specific indication(s) and the reasons why. DGDA may choose to mention in the product information the biosimilar product nature of the product, the studies that have been performed with the biosimilar product and the specific reference product, and/or to include instructions for the prescribing physician on how to use biosimilar product.

11. ROLE AND RESPONSIBILITIES OF DIRECTORATE GENERAL OF DRUG ADMINISTRATION

One of the responsibilities of the DGDA is to set up appropriate regulatory oversight for the licensing and post-marketing surveillance of biosimilar product that are developed and/ or authorized for use in its area of jurisdiction. The experience and expertise of the DGDA in evaluating bio-therapeutic products is a key prerequisite for appropriate regulatory oversight of these products. The DGDA is responsible for determining a suitable regulatory framework for

licensing biosimilar product. It may choose to use or amend existing pathways or to develop a new pathway for this purpose.

12. REFERENCES

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- 2) Requirements for the use of animal cells as in vitro substrates for the production of biologicals. In: WHO Expert Committee on Biological Standardization. Forty-seventh report. Geneva, World Health Organization, 1998, Annex 1 (WHO Technical Report Series No. 878).
- 3) WHO reference materials for cytokines/growth factors and endocrinological substances (available on the internet at <http://www.who.int/bloodproducts/Catalogue/en/index.html>). 4)Article 10(4) of Directive 2001/83/EC, as amended.
- 4) EMEA guidelines on Similar Biological Medicinal Products. (EMEA/CHMP/437/04, 2005).
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- 6) EMEA guidelines on Similar Biological Medicinal Products containing Biotechnology-derived Proteins as Active Substance: Non-clinical and Clinical Issues. (EMEA/CHMP/BMWP/42832, 2006).
- 7) Biosimilar meeting Report:

http://www.who.int/biologicals/areas/biological_therapeutics/Final13September2007.pdf
- 8) Meeting report on WHO Informal Consultation on International Non-proprietary Names (INN) Policy for Biosimilar Products, 4-5 September, Geneva, 2006 (INN working report 07.211) (available on the Internet at (http://www.who.int/medicines/services/inn/BiosimilarsINN_ReportSept2006.pdf))
- 9) Good Manufacturing Practice for Biological Products (WHO TRS No. 822, 1992)

- 10) ICH guidelines on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (S6, 1997).
- 11) ICH guidelines on Statistical Principles for Clinical Trials (E9, 1998)
- 12) ICH guidelines on Choice of Control group and Related Issues in Clinical Trials (E10, 2000)
- 13) EMEA guidelines on Immunogenicity Assessment of Biotechnology-derived therapeutic proteins. (EMEA/CHMP/BMWP/ 14327, 2007)
- 14) ICH guidelines on Pharmacovigilance planning (E2E, 2004)
- 15) ICH guidelines on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (Q5C, 1995)
- 16) ICH guidelines on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Q6B, 1998)
- 17) Regulations on Review & Authorization of Biological Products (KFDA Notification No. 2009-59)
- 18) Regulations on Validation of Drug Products (KFDA Notification No. 2009-10)
- 19) Guidelines on Validation of Analytical Procedures for Drug Products (KFDA, 2004)
- 20) Handbook for Interpretation and Application of the Guidelines on Validation of Analytical Procedures for Drug Products (KFDA, 2008)
- 21) Guidelines on Safety Studies of Biological Products (KFDA, 2008)
- 22) Guidelines on Evaluation of Changes to Manufacturing Processes for Biological Products (KFDA, 2009)
- 23) Guidelines on similar biologics: Regulatory requirements for marketing authorization in India.

Annexure 1:

Registration process flow for biosimilar products manufactured by imported bulk

Steps for registration:

1. NOC to import samples for R&D.
2. Source validation for biosimilars:
 - a) Principal company profile.
 - b) Copy of valid manufacturing license.
 - c) GMP certificate issued by the licensing authority of country of origin. If local GMP certificate is not available, then DGDA may perform onsite audit.
 - d) List of countries where they export the same API.
 - e) Certificate of Analysis (COA) with specification of each API.
 - f) Comparability study report (Physicochemical and Biological with reference product)
 - g) List of products of the Principal Company by the Licensing Authority of country of origin.
 - h) Form-9 signed by authorized person of Principal Company including the name of the API.
 - i) Clinical trial report from bulk manufacturer or Satisfactory clinical trial report conducted in Bangladesh or other country with reference product.
3. Recipe submission:

Necessary documents

- a) Data generated from development of R& D batch.
- b) Analytical method development.
- c) Process development.
- d) 3-month stability (R&D batch).

4. Application for annexure with below documents:

- a) Product physiochemical profile (compositional and structural analysis)
- b) Reference material characterization.
- c) Test method qualification (linearity, precision, accuracy, specificity)
- d) Test method validation (robustness, stability-indicating capability)
- e) COA of bulk material manufacturer.
- f) In house testing and full quantification certificate (corresponding COA).
- g) Formulation screening (excipient selection, formulation stability)
- h) Finished product specifications (Pharmacopoeia / ICH 6B / example of annexure 4)
- i) Finished Product testing, COA.
- j) Process validation protocol and subsequent submission of data. (proof of consistency in process)
- k) Stability testing (accelerated and ongoing real-time/real condition, at least 3 batches data.)
- l) Extractable/Leachable studies based on available public data.

5. After approval of annexure, subsequently approval of Packaging materials, Price and then MAH certificate is issued.

6. Post marketing documents:

- a) Real time Stability data up to shelf-life
- b) Post marketing observational study report on reasonable number of subjects within 6 months to 1 yr.
- c) Any change should be submitted as per ICH Q5E guideline.

Annexure 2:

Registration process flow for Indigenous or locally developed Biosimilar products:

Steps for registration:

1. Application for NOC to import host cell / cell line / master cell
 - a. Host cell / cell line / master cell Identification and characteristics document
 - b. Certificate of analysis

2. Application to DGDA to start preclinical study
 - 2.1 Information about product development
 - a) Preparation / establish of cell bank.
 - b) Procedure to prepare working cell bank.
 - c) Data generated from development of R& D batch, manufacturing flow chart, cell bank history, and preliminary characterization and manufacturing process in brief.
 - d) Analytical specifications.
 - e) Comparability exercise.

 - 2.2 Information about preclinical study
 - a) Protocol for pre-clinical study for local study or NOC to send sample overseas.

3. Information about production of clinical lot.
 - a) Pre-clinical study report.
 - b) Analytical methods.
 - c) 3 months stability studies of developmental batch.

4. Application to DGDA for permission to start clinical trials

4.1 If clinical trials be conducted in overseas, application to DGDA for NOC to send sample.

4.2 If clinical trials be conducted in Bangladesh, application to DGDA for permission to start clinical trials with following documents:

- a) DGDA approval certificate for CRO.
- b) Approved Protocol by BMRC (within 3 months) /IRB/IEC (after 3 months)
- c) Investigator's Brochure.
- d) Informed Consent Form.
- e) Copy of signed agreement with sponsor.
- f) CV of Principal Investigator & his/her Team Members
- g) Whether they have GCP training.
- h) List of SOPs.
- i) GMP certificate of the manufacturing plant.
- j) Test Samples, COA, Summary Protocol.

5. Application for Marketing Authorization (Annexure Approval)

- a) DGDA format CTD dossier for all 5 modules.
- b) Clinical trial full report

6. After approval of annexure, subsequently approval of Packaging materials, Price and then MAH certificate is issued.

7. Post marketing documents:

- a) Real time stability data up to shelf-life
- b) Post marketing observational study report on reasonable number of subjects within 6 months to 1 yr.
- c) Any change should be submitted as per ICH Q5E guideline

Annexure 3:

Registration process flow for imported biosimilar products:

Steps for registration:

1. COPP from one of the 7 developed countries like USA, France, Germany, UK, Switzerland, Japan, Australia or EMA certificate.
2. Certificate of Analysis (COA).
3. Temperature monitoring record, such as data logger report, shipment validation report.
4. Local agent must submit proof of availability of cold chain storage and supply facilities.
5. Samples and packaging material submission.

Annexure 4: Requirement of Physicochemical and Biological Characterization.

4A. Physicochemical and biological characterization of nucleic acid based recombinant products.

Nucleic acid based recombinant products - Physicochemical	Nucleic acid based recombinant products - Biological
<ul style="list-style-type: none"> • Sequence (To prove if the sequence same as reference biologic). • Restriction map for > 1000 bp (To check if secondary structure is same as reference biologic). • Purity on HPLC (To check if any impurities are there). • Gel electrophoresis (agarose / acrylamide / urea page) (To check quality of sample). 	<p>Vector for expression of recombinant protein</p> <ul style="list-style-type: none"> • Expression pattern in suitable target host cell (To compare efficiency of expression of similar biologic with reference biologic in the target cell). • Expression pattern in suitable animal species upon administration (along with vehicle as negative control) (To compare efficiency of expression of similar biologic with reference biologic in the target cell when administered in whole animal, this will evaluate the efficiency of vector location and promoter activity in target cell). • Kinetics of expression during the proposed therapeutic period of protection (To compare half-life of the similar biologic with reference biologic).

Nucleic acid based recombinant products - Physicochemical	Nucleic acid based recombinant products - Biological
<ul style="list-style-type: none"> • Western / Southern / Northern blot (Confirmation with reference biologic). • Absorption spectrum from 190 to 800 nm (To check similarity to reference biologic). • CD spectrum from 190 to 800 nm (To check secondary structural changes if any due to binding of impurities). • Hybridization to the target sequence. (To confirm with reference biologic). 	<ul style="list-style-type: none"> • Efficacy in appropriate model <i>in vitro</i> and / or <i>in vivo</i> (To compare therapeutic activity of the similar biologic with reference biologic). • Absence of interference of marker enzyme / antibiotic, if any (To compare therapeutic interference and toxicity due to a marker in the similar biologic with that of reference biologic). <p>Vector for expression of siRNA / snRNA etc.</p> <ul style="list-style-type: none"> • Expression pattern in suitable target host cell (To compare efficiency of expression of similar biologic with reference biologic in the target cell). • Expression pattern in suitable animal species upon administration (along with vehicle as negative control) (To compare efficiency of expression of similar biologic with reference biologic in the target cell when administered in whole animal, this will evaluate the efficiency of vector location and promoter activity in target cell).

Nucleic acid based recombinant products - Physicochemical	Nucleic acid based recombinant products - Biological
<ul style="list-style-type: none"> • T_m profile (To check if any impurities are present). • Quantification of RNA and DNA using nanodrop / other technology or reagent (To check concentration and impurity, if any). 	<ul style="list-style-type: none"> • Kinetics of expression during the proposed therapeutic period of protection (To compare half-life of the similar biologic with reference biologic). • Efficacy in appropriate model <i>in vitro</i> and / or <i>in vivo</i> (To compare therapeutic activity of the similar biologic with reference biologic). • Absence of interference of marker enzyme / antibiotic if any (To compare therapeutic interference and toxicity due to a marker in the similar biologic with that of reference biologic).

4B. Physicochemical and biological characterization of therapeutic proteins.

Therapeutic Proteins – Physicochemical	Therapeutic Proteins - Biological
<ul style="list-style-type: none"> • Appearance, Particulates, pH, osmolality, particle size (if applicable) (To check homogeneity). • MW, Sequence and amino acid composition (To check purity). • N terminal sequence (at least 20 amino acid) (To check amino acid sequence and structure). • Glycosylation, Phosphorylation, Acetylation, and Myristoylation, if any (To check if active / inactive form). • PEGylation, esterification, if applicable (To check if modification is appropriate). • Tryptic map (1D and 2D) (To check if secondary structure is conserved). • Sulfhydryl group(s) and disulphide bridges (To check if secondary structure is conserved). • Size and Purity on HPLC (RP, SEC, 	<ul style="list-style-type: none"> • Biological activity in suitable host cell (To compare activity of protein in similar biologic with reference biologic in the target cell). • Biological activity in suitable animal species (if available) upon administration (along with vehicle as negative control) (To compare activity of similar biologic with reference biologic in the target cell when administered in whole animal, this will evaluate the efficiency of vector location and promoter activity in target cell). • Kinetic of biological activity during the proposed therapeutic period of protection (To compare half-life of the similar biologic with reference biologic). • Efficacy in appropriate model <i>in vitro</i> and / or <i>in vivo</i> (if available) (To compare therapeutic interference and toxicity due to a marker in the similar biologic with that of reference biologic).

<p>IEX) / Mass spectrometry (To check if it is homogeneous and no impurities are present).</p> <ul style="list-style-type: none">• Isoform pattern, if any (To check if secondary structure is conserved).• Gel electrophoresis (IEF, SDS PAGE and Native PAGE), Western blot (To qualitative check purity / nativity).• Absorption spectrum from 190 to 800 nm (molar absorptivity) (To check purity).• CD spectrum from 190 to 800 nm (To check if secondary structure is conserved)• Fluorescence spectrum (To check if any impurities such as quenchers are present).• FTIR spectrum, if applicable (To check in any prosthetic group is present).• NMR spectrum, if applicable (To check if any prosthetic group is present).• Affinity to the target receptor (To check if required affinity to receptor is conserved).• Helix to Coil Transition profile (To verify if the preparation is stable and impurities or isoforms are affecting the stability).	
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4C. Physicochemical and biological characterization of therapeutic enzymes.

Therapeutic Enzymes - Physicochemical	Therapeutic Enzymes – Biological
<ul style="list-style-type: none"> • Appearance, particulates, pH, osmolality, particle size (if applicable) (To check homogeneity). • Sequence and amino acid composition (To check purity). • Glycosylation, phosphorylation, acetylation and myristoylation, if any (To check if active / in active form) • PEGylation, esterification, if applicable (To check if modification is appropriate). • Tryptic peptide map (1D and 2D) (To check if secondary structure is conserved). • Size and purity on HPLC (RP, SEC, IEX) / Mass spectrometry (To check if secondary structure is conserved). • Gel electrophoresis (IEF, SDS PAGE and Native PAGE), Western blot (To qualitatively check purity / nativity). • Enzyme activity in gel assay in presence of chromogenic substrate (To check activity). • Absorption spectrum from 190 to 800 nm (To check purity). 	<ul style="list-style-type: none"> • Biological activity in suitable target host cell (To compare activity of enzyme in similar biologic with reference biologic in the target cell). • Biological activity in suitable animal species upon administration (along with vehicle as negative control) (To compare activity of similar biologic with reference biologic in the target cell when administered in whole animal, this will evaluate the efficiency of vector location and promoter activity in target cell). • Kinetics of biological activity during the proposed therapeutic period of protection (To compare half-life of the similar biologic with reference biologic). • Efficacy in appropriate model <i>in vitro</i> / or <i>in vivo</i> (To compare therapeutic interference and toxicity due to a marker in the similar biologic with that of reference biologic).

Therapeutic Enzymes - Physicochemical	Therapeutic Enzymes – Biological
<ul style="list-style-type: none"> • CD spectrum from 190 to 800 nm (To check if secondary structure is conserved). • Helix to Coil Transition profile (To verify if the preparation is stable and impurities or isoforms are affecting the stability). • Fluorescence spectrum (To check if any impurities such as quenchers are present). • Km with natural substrate (To check homogeneity of biosimilar interaction with active site same as reference biologic with reference to known substrates). • Ki with known inhibitors (1/2) (To check comparability of competitive biosimilar interaction with active site same as reference biologic with reference to known inhibitors). 	

4D. Physicochemical and biological characterization of antibodies

Antibodies – Physicochemical	Antibodies – Biological
<ul style="list-style-type: none"> • Sequence and amino acid composition (To check purity). • Tryptic map (1D and 2D) (To check if secondary structure is conserved). • Light and heavy chain separation (To check antigenic recognition motif). • IgG type (To check specificity of IgG in localization of specific tissues / plasma). • Purity on HPLC (RP, SEC, IEX)/ Mass spectrometry (To check if preparation is free of any impurities). • Gel electrophoresis (IEF, SDS PAGE and Native PAGE), Western blot (To check quality purity difference). • Absorption spectrum from 190 to 800 nm (To check purity). 	<ul style="list-style-type: none"> • Neutralizing activity in suitable target host cell (at least one highly prevalent local variant / isolate should be used) (To compare activity of similar biologic with reference biologic in the target cell). • Neutralizing activity in suitable animal species (if feasible) upon administration (along with vehicle as negative control) (at least one highly prevalent local variant / isolate should be used) (To compare activity of similar biologic with reference biologic in the target cell when administered in whole animal, this will evaluate the efficiency of vector / antibody location and promoter activity in target cell). • Kinetics of neutralizing activity during the proposed therapeutic period of protection (at least one highly prevalent local variant/ isolate should be used) (To compare half-life of the similar biologic with reference biologic).

Antibodies – Physicochemical	Antibodies – Biological
<ul style="list-style-type: none"> • CD spectrum from 190 to 800 nm (To check if secondary structure is conserved). • Helix to Coil Transition profiles (To verify if the preparation is stable and impurities or isoforms are affecting the stability). • Epitopic mapping of the antibody binding to specific and non-specific epitopes with antigenic variant isolated from local isolates (To check specificity profile of similar biologic with reference biologic in epitope recognition, particularly in recognition of local variant of a host cell protein or infectious agent coded protein). • Anti-body dilution factors in neutralization (To check symbol with reference biologic in the neutralization strength of the antibody preparation). 	<ul style="list-style-type: none"> • Efficacy in appropriate disease/ infection model <i>in vitro</i> and/ or <i>in vivo</i> (if available) (To compare therapeutic interference and toxicity due to a marker in the similar biologic with that of reference biologic).

Annexure 5:

General equipment list for biosimilars manufacturing.

a) General list of equipment for biosimilar API manufacturing.

1. Balance.
2. pH meter.
3. Viscometer.
4. Osmometer.
5. Bioreactor.
6. Centrifugation system.
7. Filtration system.
8. Different types of chromatography system.
9. Incubator.
10. Shaker.
11. Microscope.
12. Spectrophotometer.
13. Biosafety cabinet.
14. Storage system, cell bank (Freezer, Refrigerator)
15. Autoclave system.
16. Water purification system.
17. Effluent Treatment Plant (ETP).

b) General list of equipment for biosimilar fill finish manufacturing

1. Mixing Vessels.
2. Sterile filtration system.
3. Filling machine for syringe.
4. Filling machine for vial.
5. Lyophilizer.
6. Sealing machine.
7. Labeling machine.

8. Blister machine.
9. Printing machine.
10. Water purification system for WFI.
11. Autoclave.
12. Balance.
13. Storage system (Freezer, Refrigerator)

Annexure 6:

General equipment list for Quality Control.

Equipment list for Quality Control

1. Spectrophotometer.
2. Image analyzer.
3. Biosafety cabinet.
4. Storage system, cell bank (Freezer, refrigerator).
5. Gel electrophoresis system (IEF, SDS PAGE)
6. Western/ Southern/ Northern blot.
7. PCR.
8. pH meter
9. Viscometer.
10. Osmometer.
11. TOC analyzer.
12. Centrifugation system.
13. HPLC
14. Shaker.
15. Incubator.
16. Autoclave system.
17. Label free molecular interaction analyzer.
18. Amino acid analyzer.
19. Sequencer.
20. Mass spectrometer.

Annexure 7:

Human resources area of expertise.

1. Biotechnology.
2. Genetic Engineering.
3. Biochemistry.
4. Molecular Biology.
5. Molecular Genetics.
6. Microbiology.
7. Bioinformatics.
8. Biostatistics.
9. Mechanical / Chemical Engineering.
10. Pharmacy
11. Chemistry.
12. Applied Chemistry.

Annexure 8: Form-9

Form 9 [Sec rule 241]

Form of undertaking to accompany an application for an import license

Whereas.....of..... intends to apply for a license under the Drugs Rules. 1945 for the import into Bangladesh of the substances specified below manufactured by us. We of..... hereby give this undertaking that for the duration of the said license -

(1) The said applicant shall be our agent for the import of the substances into Bangladesh;

(2) We shall comply with the conditions imposed on a licensee by clauses (a) to (e) of Rule 78 of Drugs Rules, 1945;

(3) We declare that we are carrying on the manufacture of the substances mentioned in this undertaking at the premises specified below and we shall from time to time report any change of premises on which the manufacture will be carried on and in cases where manufacture is carried on in more than one factory any change in the distribution of functions between the factories;

(4) We shall comply with the provisions of Part IX of the Drugs Rules, 1945:

(5) Every substance manufactured by us for import under license into Bangladesh shall as regards strength. quality and purity conform with the provisions of Chapter III of the Drugs Act, 1940 and of the Drugs Rules, 1945;

(6) We shall comply with such further requirements, if any, as may be specified by rules made by the central government under the Act and of which the licensing authority has given to the licensee not less than four months' notice.

List of Substances

Particulars of premises where manufacture is carried on.

Date: Signed by or on behalf of the manufacturer.....

Amended *vide* Ministry of Health and Works (Health Division) Notification No F. 27.34/49.M. S. & G. dated the 21st September. 1950.