National Agency for Food & Drug Administration &Control (NAFDAC)

Drug Registration & Regulatory Affairs (DR&R)Directorate

BIOSIMILAR GUIDANCE DOCUMENT

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Chapter 1 : Introduction and Important Considerations

Biotechnological products are protein molecules derived from biotechnology methods or other cutting-edge technologies. They were introduced on the market in the early 1980s, setting new milestones in modern pharmaceutical therapy that improve the quality of life for many patients with life-threatening, serious, chronic and debilitating diseases. Today, the so-called similar biotechnological products (also known as biosimilars), their first-generation successors, have gone into medical application.

Biologics are large, highly complex molecular entities manufactured using living cells and are inherently variable. Their manufacturing process is highly complex and critical to defining the characteristics of the final product. Maintaining batch-to-batch consistency is a challenge. Subtle variations in the production, or even transport or storage conditions, may potentially result in an altered quality, safety and efficacy profile of the final product. Hence, the phrase, "process is the product" is often used in reference to biologics.

Biotherapeutic products have a successful record in treating many life threatening and chronic diseases. However, their cost has often been high, thereby limiting their access to patients, particularly in developing countries. Recently, the expiration of patents and/or data protection for the first major group of originator's biotherapeutics has ushered in an era of products that are designed to be 'similar' to a licensed originator product. These products rely, in part, for their registration on prior information regarding quality, safety and efficacy obtained with the originator products. The clinical experience and established safety profile of the originator products should contribute to the development of Biosimilars. A variety of terms, such as 'similar biotherapeutic products , 'follow-on protein products', 'follow-on biologics' and 'subsequent-entry biologics' have been used by different jurisdictions to describe these products.

As part of its mandate for assuring quality, safety and efficacy of regulated products in Nigeria, the National Agency for Food and Drug Administration and Control (NAFDAC) sets nationally accepted norms and standards for the evaluation of these products. Written standards established through the Expert Committee on Biological Standardization (ECBS) of the World Health Organization (WHO) serve as a basis for setting national requirements for the overall regulation of biosimilars.

An increasingly wide range of biosimilars are under development or are already licensed in many countries and a need for guidelines for their evaluation and overall regulation was formally recognized by the WHO in 2007. This document is intended to provide guidance for the development and evaluation of such products.

It is essential that the standard of evidence supporting the decisions to license biosimilars be sufficient to ensure that the product meets acceptable levels of quality, safety and efficacy to ensure public health. Also, it is expected that the elaboration of the data requirements and considerations for the registration of these products will facilitate development of and increased access to biosimilars of assured quality, safety and efficacy at more affordable prices. In most cases, their authorization will be evaluated on a case-by-case basis, and the amount of data required by NAFDAC may vary.

It is important to note that biosimilars which are not shown to be similar to a Reference Biotherapeutic Product (RBP) as indicated in this guideline should not be described as 'similar', nor called a biosimilar. Such products could be licensed through the usual processes using a more extensive non-clinical and clinical data set before full registration application.

It was recognized that some important issues associated with the use of biosimilars shall be defined by NAFDAC. They include but are not limited to the following:

- Intellectual property issues;
- Interchangeability and substitution of biosimilar with RBP; and biosimilar with another Biosimilar;
- Labeling and prescribing information.

1.1 Aim

The intention of this document is to provide acceptable principles for registration of biosimilar products that are claimed to be similar to RBP of assured quality, safety, and efficacy that have been licensed based on a full registration dossier by a stringent Regulatory Authority. On the basis of proven similarity, the registration of a biosimilar will rely, in part, on non-clinical and clinical data generated with an already licensed RBP.

1.2 Guiding Principles

Our primary objective is public health protection and patient safety. Biosimilars should meet the same standards of quality, safety and efficacy as any other registered biotechnological product. The regulatory paradigm for biosimilars is not intended to be too onerous, too stringent or too loose rather we undertake a cautious and balanced approach.

Our experience demonstrates that transparent and open dialogue with all relevant stakeholders is key to put in place a robust and responsive regulatory framework in this

emerging field whilst creating and promoting a patient-oriented, innovative and favourable regulatory environment. In corollary this will further enhance and promote a dynamic and competitive knowledge-based economy for healthcare biotechnology in Nigeria.

1.3 Scope and Application

The concept of biosimilarity applies to biotechnology drug licensing submissions in which the manufacturer would, based on demonstrated similarity to a RBP, rely in part on publicly available information from a previously approved biotechnological product in order to present a reduced non-clinical and clinical package as part of submission.
The demonstration of similarity depends upon detailed and comprehensive product characterization, therefore, information requirements outlined within this document apply to biotechnological product that contain, as the active substances, well characterized proteins derived through modern biotechnological methods such as recombinant DNA, into microbial or cell culture.

The rationale for creating the new regulatory paradigm for biosimilars is that biotherapeutics / biologics similar to a reference product do not usually meet all the conditions to be considered as a generic. The term "generic medicine" refers to chemically-derived products which are identical and therapeutically equivalent to the originator product, For such generics, demonstration of bioequivalence with the originator product is usually appropriate to infer therapeutic equivalence.

However, it is unlikely that biotherapeutics can generally follow this standard approach for generics because of their large and complex molecular structures, which are more difficult to adequately characterize in the laboratory.

Based on the current analytical techniques, two biotherapeutics produced by different manufacturing processes cannot be shown to be totally identical, but similar at best.

For these reasons, the standard generic approach is scientifically not applicable to development of biosimilar products and additional non-clinical and clinical data are usually required.

Based on the comparability approach and when supported by analytical systems, the comparability exercise at the quality level may allow a reduction of the non-clinical and clinical data requirements compared to a full dossier. This in turn, depends on the clinical experience with the substance class and will be a case by case approach.
The biosimilar approach does not cover complex biologics such as blood-derived products, vaccines, immunologicals and gene and cell therapy products.

Whether a product would be acceptable using the biosimilar paradigm depends on the analytical procedures, the manufacturing process employed, as well as clinical and regulatory experiences.

1.4 Policy Statements

The following policy statements outline the fundamental concepts and principles constituting the basis of the regulatory framework for biosimilars:

1.4.1 In implementing this guidance document, the Guidelines on biosimilars, will be used as the basis for defining the registration requirements and / or process for registration of biosimilars in Nigeria.

1.4.2 Biosimilars are not generic biologics / biogenerics. Thus, the classic generic paradigm (i.e demonstration of bioequivalence of the generic drug with the reference product is usually appropriate to infer therapeutic equivalence) and

many characteristics associated with approval process used for generic drugs do not apply to biosimilars.

1.4.3 Approval of a product through the biosimilar pathway is not an indication that the biosimilar may be automatically substituted with its reference product or other biosimilar. The decision for substitutability with the reference product shall be based on science and clinical data.

1.4.4 A biosimilar product cannot be used as a reference product by another manufacturer because a reference product has to be approved on the basis of a complete/full quality and clinical data package.

1.4.5 Eligibility for a biosimilar pathway hinges on the ability to demonstrate similarity to a reference product. Product employing clearly different approaches to manufacture from the reference product (for example use of transgenic organisms versus cell culture) will not be eligible for the regulatory pathway for biosimilars.

1.4.6 The manufacturer must conduct a direct and extensive comparability exercise between its product and the reference product, in order to demonstrate that the two products have a similar profile in terms of quality, safety and efficacy. Only one reference product is allowed throughout this exercise. **The rationale for the choice of reference product should be provided by the manufacturer to the NRA**.

1.4.7 Non-clinical and clinical requirements outlined for biosimilar submission in this guidance document must demonstrate similarity to the reference product, based on results of the comparability exercises from Chemistry, Manufacturing and control (CMC) perspectives. When similarity of a biosimilar cannot be adequately established, the submission of such a product should be as a 'Stand-alone' **biotechnological product with complete non-clinical and clinical data**.

1.4.8 It should be recognized that there may be subtle differences between biosimilars from different manufacturers or compared with reference products, which may

not be fully apparent until greater experience in their use have been established. Therefore, in order to support Pharmacovigilance monitoring, the specific biosimilar given to patient should be clearly identified.

1.4.9 It was acknowledged that although International Non-proprietary Names (INNs) served as a useful tool in worldwide Pharmacovigilance, for biologicals they could not be relied upon as the only means neither of product identification, nor as an indicator of the interchangeability of biologicals in particular biosimilars.

1.4.10 A biosimilar manufacturer that is not from a jurisdiction that formally adopts International Conference on Harmonization (ICH) guidelines, a current Good Manufacturing Practice (cGMP) audit of the manufacturing facilities is required.

1.5 Scientific considerations and Concept for Registration of Biosimilars

For the registration of generic medicines, the regulatory framework is well-established in most countries. Demonstration of structural similarity and bioequivalence of the generic medicine with the reference product is usually appropriate to infer (conclude) therapeutic equivalence between the generic and the reference product. However, the generic approach is not suitable for the registration of biosimilars since biotherapeutic products usually consist of relatively large and complex entities that are difficult to characterize. In addition, biosimilars are manufactured and controlled according to their own development since the manufacturer of a biosimilar normally does not have access to all the necessary manufacturing information on the originator product. However, even minor differences in the manufacturing process may affect the pharmacokinetics, pharmacodynamics, efficacy and/or safety of biotherapeutic products. As a result, it has been agreed that the normal method for registration of generic medicines through bioequivalence studies alone is not scientifically appropriate for biosimilars.

Decision making regarding the registration of biosimilars should be based on scientific evidence. The onus is on a manufacturer of a biosimilar to provide the necessary

evidence to support all aspects of an application for registration. As with any drug development program, the development of a biosimilar involves a stepwise approach starting with characterization and evaluation of quality attributes of the product and followed by non-clinical and clinical studies. **Comprehensive characterization and comparison at the quality level are the basis for possible data reduction in the non-clinical and clinical development.** If differences between the biosimilars and the RBP are found at any step, the underlying reasons for the differences should be investigated. Differences should always be explained and justified and may lead to the requirement of additional data (e.g. safety data).

In addition to the quality data, biosimilars require non-clinical and clinical data generated with the product itself. **The amount of non-clinical and clinical data considered necessary will depend on the product or class of products, the extent of characterization possibly done using analytical methods, on observed or potential differences between the biosimilar and the RBP, and on the clinical experience with the product class (*e.g.* safety/immunogenicity concerns in a specific indication).**

The ability for the biosimilar to be approved based on reduced non-clinical and clinical data depends on proof of its similarity to an appropriate named RBP through the comparability exercise. Manufacturers should demonstrate a full understanding of their product, consistent and robust manufacture of their product, and submit a full quality dossier that includes a complete characterization of the product. The comparability exercise between the biosimilar and the RBP in the quality part represents an additional element to the 'traditional' full quality dossier. The reduction in data requirements is therefore only possible for the non-clinical and/or clinical parts of the development program. The dosage form and route of administration of the biosimilar should be the same as for the RBP.

Studies must be comparative in nature employing analytical strategies (methods) that are sensitive to detect potential differences between the biosimilar and the RBP. The main clinical studies should use the final formulation derived from the final process material of the biosimilar. Otherwise, additional evidence of comparability will be required to demonstrate that the biosimilar to be marketed is comparable to that used in the main clinical studies.

If similarity between the biosimilar and the RBP has been convincingly demonstrated, the biosimilar may be approved for use in other clinical indications of the RBP that have not directly been tested in clinical trials if appropriate scientific (clinical & non-clinical) justification for such extrapolation is provided by the manufacturer. Significant differences between the biosimilars and the RBP detected during the comparability exercise would be an indication that the products are not similar and more extensive, non-clinical and clinical data may be required to support the application for registration.

1.6 Comparability Exercise

The comparability exercise for a biosimilar is designed to show that the product has highly similar quality attributes when compared to the RBP. However, it also includes the non-clinical and clinical studies to provide an integrated set of comparative data. The comparability data for safety, efficacy and quality can be considered to be an additional set of data over that which is normally required for an originator product developed as a new and independent product. This is the basis for reducing the non-clinical and clinical data requirements.

Although the quality comparisons are undertaken at various points throughout the quality application / dossier, a distinction should be made between usual quality data

requirements and those presented as part of the comparability exercises. It may be useful to present these as a separate section in the quality module.

1.7 Key Principles for the Registration of Biosimilars

a. The development of a biosimilar product involves stepwise comparability exercise(s) starting with comparison of the quality characteristics of the biosimilar and RBP. Demonstration of similarity of a biosimilar product to a RBP in terms of quality is a prerequisite for the reduction of the non-clinical and clinical data set required for registration. After each step of the comparability exercise, the decision to proceed further with the development of the biosimilar should be evaluated.

b. The basis for registering a product as a Biosimilar product depends on its demonstrated similarity to a suitable RBP in quality, non-clinical, and clinical parameters. The decision to register a product as a biosimilar should be based on evaluation of the whole data package for each of these parameters.

c. If relevant differences are found in the quality, non-clinical, or clinical studies, the product will not likely qualify as a biosimilar and a more extensive non-clinical and clinical data set will likely be required to support its application for registration. Such a product should not qualify as a biosimilar as defined in this guideline.

d. If comparability exercises and/or studies with the RBP are not performed throughout the development process as outlined in this guidance document, the final product should not be referred to as a biosimilar.

e. Biosimilas are not "generic medicines" and many characteristics associated with the authorization process generally do not apply.

f. Biosimilars, like other biotherapeutic products, require effective regulatory oversight for the management of their potential risks and in order to maximize their benefits.

1.8 Reference Biotherapeutic Product

Comprehensive information on the RBP provides the basis for establishing the safety, quality, and effectiveness profile to which the biosimilar is compared. The RBP also provides the basis for dose selection and route of administration, and is utilized in the comparability studies required to support the registration application. The demonstration of an acceptable level of similarity between the biosimilar and RBP provides the rationale for utilizing a reduced non-clinical and clinical data set to support the application for market authorization of the biosimilar. Hence the RBP is central to the registration of a biosimilar.

To support registration of the biosimlars, similarity of the product to the RBP should be demonstrated through head-to-head comparability with the RBP. The same RBP should be used throughout the entire comparability exercise.

The choice of a RBP is of critical importance for the evaluation of biosimilars. The rationale for the choice of the RBP should be provided by the manufacturer of the biosimilars in the submission to NAFDAC.
NAFDAC has criteria to guide their acceptability of registering of biosimilars. The use of reference products with proven efficacy and safety in a given population will be one of the factors to consider. Another parameter will be post marketing safety experience in addition to the duration and marketed indication.

1.9 Considerations for Choice of Reference Biotherapeutic Product(RBP).

1) The RBP should have been registered on the basis of a full registration dossier in Nigeria and / or by a stringent Regulatory Authority for a suitable duration and have been used such that the demonstration of similarity to it brings into relevance a substantial body of acceptable data regarding the safety and efficacy.

2) The manufacturer needs to demonstrate that the chosen RBP is suitable to support the application for registration / marketing authorization of a biosimilar.

3) The RBP should be registered based on a full quality, safety, and efficacy data. Therefore a biosimilar should not be considered as a choice for RBP.

4) The same RBP should be used throughout the development of the biosimilar (i.e. for the comparative quality, non-clinical, and clinical studies).

5) The drug substance of the RBP and the biosimilar must be shown to be similar.

6) The dosage form and route of administration of the biosimilar should be the same as that of the RBP.

Note: Appropriate Circumstances for the Use of a Reference Biotechnology Product (RBP) not licensed in Nigeria

In instances where the RBP used is not licensed in Nigeria, the following should be considered:

a. The applicant is responsible for showing that the RBP not licensed in Nigeria, used for the purposes of demonstrating similarity is registered in a jurisdiction that formally adopts International Conference on Harmonization (ICH) guidelines and has regulatory standards and principles for evaluation of medicines, post-market surveillance activities, and approach to comparability that are similar to Nigeria;

b. The applicant has the responsibility of ensuring that the chosen RBP not licensed in Nigeria has associated with it sufficient information and data to support the submission;

c. The RBP not licensed in Nigeria is from a jurisdiction that has an established relationship with Nigeria; and

1.10 Extrapolation of Efficacy and Safety Data to other Clinical Indications

If similar efficacy and safety of the biosimilar and RBP have been demonstrated for a particular clinical indication, extrapolation of these data to other indications of the RBP (not studied in independent clinical studies with the biosimilar) may be possible if all of the following conditions are fulfilled:

i. A sensitive clinical test model has been used that is able to detect potential differences between the biosimilar and the RBP;

ii. The clinically relevant mechanism of action and/or involved receptor(s) are the same; e.g. Growth Hormone (GH) action in different conditions of short stature in children; erythropoiesis-stimulating action of epoetins in different conditions associated with anaemia or for the purpose of autologous blood donation. If the mechanism of action is different or not known a strong scientific rationale and additional clinical data will be needed;

iii. Safety and immunogenicity of the biosimilar have been sufficiently characterized and there are no unique/additional safety issues expected for the extrapolated indication(s), for which clinical data on the biosimilar are not being provided; e.g. immunogenicity data in immunosuppressed patients would not allow extrapolation to an indication in healthy subjects or patients with autoimmune diseases while the reverse would be valid;

iv. If the efficacy trial used a non-inferiority study design and demonstrated acceptable safety and efficacy of the biosimilar compared to the RBP, the applicant should provide convincing arguments that this finding can be applied to the extrapolated indications; e.g. results from a non-inferiority trial in an indication where a low dose is used may be difficult to extrapolate to an indication where a higher dose is used, from both efficacy and safety point of view.

If these prerequisites for extrapolation of efficacy and safety data of the biosimilar to other indication(s) of the RBP are not fulfilled, the manufacturer **will need to submit their own clinical data to support the desired indication(s)**.

If extrapolation of results from clinical studies for one indication to one or more different indications is intended, a detailed scientific discussion on the benefit/ risk of such a proposal should be provided based on the above criteria.

1.11 Interchangeability and Substitution

This remains a controversial issue among different regulators worldwide and all concerned parties. Biosimilars are protein therapies, similar to indigenous human mediators, given in microgram quantities, not exact copies of an original medicine, with limited clinical experience at approval. Although interchangeability and substitution are not encouraged and can be detrimental to pharmacovigilance and risk management, there could be situations (financial, availability, intolerability, hospital or country necessities) when they are needed. It is generally viewed that changing or substituting a protein medicine produced by rDNA technology, whether original (innovator) or a biosimilar, is the decision of the physician and the patient when the physician explains to the patient the possibility of such substitution and examines the risks versus benefits. Physicians and pharmacist should discuss the issue before talking to the patient to

prevent inappropriate substitution. Pharmacists cannot substitute biosimilars without such consultations with physicians.

However, NAFDAC strongly recommends the followings:

(1) Changing from an innovator drug to a biosimilar which used the same innovator drug as its RBP for comparability can be accepted after physician and patient discussion.

(2) Changing from a biosimilar to another same biosimilar drug from a different manufacturer can be accepted after physician and patient discussion **only** if they both used the same RBP for comparability purposes.

(3) Changing from an innovator drug to another innovator drug for the same indication, or from a biosimilar drug to another biosimilar drug which did not use the same innovator drug as a RBP for comparability is **not acceptable** in ordinary situation. In extreme situations, physician and patient discussion, as well as hospital administration involvement in the decision for change are mandatory.

In all cases, close monitoring of the patient's responses should be performed when interchangeability or substitution is warranted, if possible on a daily basis until results are satisfactory and stable. Dosage and route of administration should be studied and adjusted when necessary. Minute differences among biosimilars and between a biosimilar and the innovator may affect the clinical outcome. In addition, and for obvious reasons, substitutions negatively affect the pharmacovigilance exercise.

1.12 Storage conditions

1.12.1 Temperature

Most finished biosimilar products need precisely defined storage temperatures.

For this reason, it is mandatory that they be transported in thermal bags to maintain the cold chain. The storage conditions for the real-time/real-temperature stability studies may be confined to the proposed storage temperature.

1.12.2 Humidity

Biosimilars are generally stored in containers protecting them from humidity. Where it can be demonstrated that the proposed containers (and conditions of storage) provides sufficient protection against high and low humidity, stability tests at different relative humidities can be omitted.

1.12.3 Accelerated and Stress Conditions

As previously noted, the shelf life should be based on real-time/real-temperature data. However, it is strongly suggested that studies be conducted on the drug substance and drug product under accelerated and stress conditions. Studies under accelerated conditions may provide useful support data for establishing the expiration date, provide product stability information for future product development (e.g., preliminary assessment of proposed manufacturing changes such as change in formulation, scale-up), assist in validation of analytical methods for the stability program, or generate information which may help elucidate the degradation profile of the drug substance or drug product. Studies under stress conditions may be useful in determining whether accidental exposures to conditions other than those proposed (e.g., during transportation) are deleterious to the

product and also for evaluating which specific test parameters may be the best indicators of product stability. Studies of the exposure of the drug substance or drug product to extreme conditions may help to reveal patterns of degradation; if so, such changes should be monitored under proposed storage conditions. While the tripartite ICH guideline on stability describes the conditions of the accelerated and stress study, the applicant should note that those conditions may not be appropriate for biotechnological/biological products. Conditions should be carefully selected on a case-by-case basis.

1.12.4 Light

Sensitivity to light as stated by the manufacturer should be indicated on the label.

1.12.5 Container/Closure

Changes in the quality of the product may occur due to the interactions between the formulated biosimilars and container/closure. Where the lack of interactions cannot be excluded in liquid products (other than sealed ampoules), stability studies should include samples maintained in the inverted or horizontal position (i.e., in contact with the closure), as well as in the upright position, to determine the effects of the closure on product quality.

Data should be supplied for all different container/closure combinations that will be marketed.

In addition to the standard data necessary for a conventional single-use vial, the manufacturer should demonstrate that the closure used with a multiple-dose vial is capable of withstanding the conditions of repeated insertions and withdrawals so that the product retains its full potency, purity, and quality for the maximum period specified in the instructions-for-use on containers, packages, and/or

package inserts. Such labeling should be in accordance with relevant NAFDAC labeling requirements.

1.12.6 Stability after Reconstitution of Freeze-dried Product

The stability of freeze-dried products, after their reconstitution, should be demonstrated for the conditions and the maximum storage period specified on containers, packages, and/or package inserts. Such labeling should be in accordance with relevant NAFDAC Drug Labeling Regulations 2005 at www.nafdac.gov.ng.

1.13 Labeling

This issue deals with the information shown on the primary or secondary package label and the inside leaflet of biosimilar. In both, the name of the product must be clearly written, with the scientific name of the product [international Non-proprietary Name, INN, if there is any designated by WHO] with the company's name and logo clearly demonstrated. For further information refer to NAFDAC Drug Labeling Regulations 2005 on www.nafdac.gov.ng.

1. The minimum labeling requirements on the primary and secondary package labels are;
   (a) Name of product- INN/scientific name and brand name (where applicable). The INN/scientific name must be written directly under the brand name and in same character.
   (b) Manufacturer's name and factory location address.
   (c) Provision for NAFDAC Registration Number.
   (d) Batch Number/Lot Number.
   (e) Manufacturing and Expiry dates.
   (f) Quantitative listing of all the active ingredients per unit dose.

(g) Precisely defined storage conditions.

2. The minimum requirements on the leaflet insert are:
   (a) Name of product- INN/scientific name and brand name (where applicable). The INN/scientific name must be written directly under the brand name and in same character.
   (b) A statement indicating that the product is a biosimilar.
   (c) The leaflet shall carry advice / caution stating that interchangeability or substitution of a biosimilar with another biosimilar or a reference biotechnology product with a biosimilar, is not advisable.
   (d) Manufacturer's name and factory location address.
   (e) Dosage regimen.
   (f) Indications, frequency, route and conditions of administration.
   (g) Quantitative listing of all the active ingredients per unit dose.
   (h) Precisely defined storage conditions.
   (i) Adequate warnings where necessary.

3. Any Biosimilar product whose name, package or label bears close resemblance to an already registered product or is likely to be mistaken for such registered product, shall not be considered for registration.

4. Any Biosimilar product which is labeled in a foreign language shall NOT be considered for registration unless an English translation is included on the label and package insert (where applicable).

5. Information on indication carried on packages and leaflet insert of product shall not differ from that in other countries, and in particular the country of origin of the product.

In addition to the above, the following specific information are also required:

i. A statement indicating that the product is a biosimilar.

ii. Key data on which the decision for market authorization will be made.

iii. The results of the comparisons between the biosimilar and RBP information on the indications approved for use should be shown.

iv. There should be no claims for bioequivalence between the biosimilar and RBP.

v. There should be no claims for clinical equivalence between the biosimilar and the RBP.

vi. Interchangeability and substitution advice should clearly and prominently stated.

vii. The brand name and the scientific name / INN of a biosimilar should be clearly stated.

viii. For all biosimilar products, precise defined storage conditions are should be clearly stated.

ix. Leaflet should include all Adverse Drug Reactions that may be associated with the use of the biosimilar.

Note: It is the duty of the Marketing Authorization Holder to inform NAFDAC of any changes to the prescribing information.

Chapter 2 : Manufacturing and Quality Consideration

The biosimilars development process, followed by a validated manufacturing process, is the start of the long pathway towards a beneficial product. Expression system, fermentation or cell culture, purification, sterilization, drug substance e.g. batch definition, pooling strategy, formulation and filling, and general parameters affecting all manufacturing steps e.g., water quality, temperature, personnel are all important elements of the process. Any manufacturing change, even among batches, can produce process-related impurities, culture/fermentation-derived impurities, purification-derived impurities, and final product-related impurities. Thus, any deviation from the RMP manufacturing (the innovator's) process may have a minor or major impact on product quality, safety, and/or efficacy. Comparing results of in-process controls of intermediates can give the first hint of such product changes. However, such comparisons will be possible only for innovators because follow-on manufacturers will not have access to the innovator's process intermediates. Deviant conformations, altered post-translational modifications, and different selections of subtype isoforms are potential consequences of process deviations that could result in altered microheterogeneity. Substitution of a single amino acid will alter biological activity. Patterns of absorption may be influenced by formulation. Finally, the batch-to-batch variability is inevitable with biologic products and contributes to comparability difficulties.

2.1 Manufacturing Process

The biosimilar product is in part defined by its own specific manufacturing process for both the drug substance and the final drug product. For a biosimilar registration in Nigeria, it would be expected that the relevant international guidelines of ICH have been considered by the manufacturer through each stage of drug development and production.

2.1.1 Comparability Consideration

The comparability exercise for a biosimilar is designed to show that the biosimilar has highly similar quality attributes when compared to the RBP. However, it also includes the non-clinical and clinical studies to provide an integrated set of comparative data. The comparability data for safety, efficacy and quality can be considered to be an additional set of data over that which is normally required for an originator product developed as a new and independent product. This is the basis for reducing the non-clinical and clinical data requirements.

Although the quality comparisons are undertaken at various points throughout the quality application/dossier, a distinction should be made between usual quality data requirements and those presented as part of the comparability exercises. It may be useful to present these as a separate section in the quality module.
Comparability studies should be performed during the manufacturing stage comparing the biosimilar under development to the RMP in all aspects including, but not limited to, qualitative and quantitative composition of the final preparation, strength and concentration, and formulation.

2.2 Quality Aspects

2.2.1 Specifications

Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval to ensure product quality and consistency. They should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.

The selection of tests to be included in the specifications is product specific and should be defined according to ICH Q6B. The rationale used to establish the proposed range of acceptance criteria should be described by the manufacturer. Each acceptance criterion should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, and by data from lots used for the manufacturing process validation, data from stability studies, relevant development data and data obtained from the quality, safety and efficacy studies.

2.2.2 Analytical Characterization

Extensive characterization studies should be applied to the biosimilar and RMP, in parallel, at both the active substance and the final medicinal product levels, to demonstrate with a high level of assurance that the quality of the biosimilar is comparable to the RMP. The direct comparison of the drug substance in the biosimilar product to a publicly available standard as a reference is not appropriate to demonstrate comparability of the drug substance. This is because the manufacturer generally does not have access to the drug substance of the RMP and since drug substance of biosimilar may not have existing and defined safety and efficacy profiles. However, the use of these standards plays an important role during development. In cases where the required analyses of quality attributes of the drug substance of the biosimilar can be made at the initial and intermediate product stages, testing of the drug product may not be needed.

2.2.3 Physicochemical Properties

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

The manufacturer should consider the concept of the desired product (and its variants) as defined in ICH Q6B when designing and conducting a comparability exercise. The

complexity of the molecular entity with respect to the degree of molecular heterogeneity should also be considered.

2.2.4 Biological Activity and Properties

Biological activity is the specific ability or capacity of the product to achieve a defined biological effect. It serves multiple purposes in the assessment of product quality and is required for characterization, and batch analysis. Ideally, the biological assay will reflect the existing mechanism of action of the protein and will thus serve as a link to clinical activity.

Thus, the use of a relevant biological assay(s) with appropriate precision and accuracy provides an important means of confirming that a significant functional difference does not exist between the biosimilar and the RBP.

For a product with multiple biological activities, manufacturers should perform, as part of product characterization, a set of relevant functional assays designed to evaluate the range of activities of the product. For example, certain proteins possess multiple functional domains that express enzymatic and receptor-binding activities. In such situations, manufacturers should evaluate and compare all relevant functional activities of the Biosimilar and RBP.

2.2.5 Purity, Impurities, and Contaminants

The purity and impurity profiles of the active substance and the final medicinal product should be assessed both qualitatively and quantitatively by a combination of analytical procedures for the biosimilar product.

2.2.5.1 The combination of analytical procedures selected should provide data to evaluate whether a change in purity profile has occurred in terms of the desired product. Where the change results in the appearance of new impurities, the new impurities should be identified and characterized when possible. Depending on the impurity type and amount, it might be appropriate to conduct

preclinical studies to confirm that there is no adverse impact on quality, safety or efficacy of the drug product.

2.2.6 Changes Introduced during Development and Post Registration

Manufacturers of biosimilar products frequently make changes to manufacturing processes of products, both during development and after approval. Reasons for such changes include but are not limited to improving the manufacturing process, increasing scale, improving product stability, and complying with changes in regulatory requirements. When changes are made to the manufacturing process, the manufacturer generally evaluates the relevant quality attributes of the product to demonstrate that modifications did not occur that would adversely impact the quality, safety and efficacy of the drug product. Such an evaluation should indicate whether or not confirmatory preclinical or clinical studies are appropriate.

When these changes are made to a process, the manufacturer should demonstrate that the associated process controls, including any new ones, provide assurance that the modified process will also be capable of providing a comparable product.
For approved products, an appropriate number of post-change batches should be analysed to demonstrate consistent performance of the process.

To support the analysis of the changes and the control strategy, the manufacturer should prepare a description of the change that summarises the pre-change and the post-change manufacturing process and that clearly highlights modifications of the process and changes in controls in a side-by-side format.

2.2.7 Stability

The stability of a product is generally highly dependent on its storage conditions, which must be clearly defined according to the product's characteristics.

Biosimilars are rather unstable structures. Most biosimilars have to be stored at 4^{o}C, and never shaken or heated.

ICH Q5C should be consulted for details on stability studies for product to product comparison.

Chapter 3 : Non-Clinical Evaluation

3.1 Introduction

This addresses the general principles for the Pre-clinical (non-clinical) development and assessment of registration applications for biosimilars containing recombinant proteins as active substance(s).

The studies to be carried out should be comparative in nature and designed to detect differences in response between the biosimilar product and the RBP. The focus will be on issues regarding biological activity, pharmacokinetics, comparability, efficacy, safety, and immunogenicity.
Pre-clinical studies may be used to highlight differences between the biosimilar product and the RMP. Such studies may have a useful role in the preliminary assessment of safety at one or more points in the development process, thus enabling clinical studies to be undertaken with greater confidence.

The applicant should justify, in the Drug Master File (DMF), the approach chosen during the development of the biosimilar and note the following:

(1) The manufacturer should demonstrate that Biosimilar is similar in terms of quality, safety and efficacy to the RMP. It may not be necessary to repeat all safety and efficacy studies if the manufacturer can demonstrate that:

(a) It is possible to characterize the product in detail with respect to physico-chemical properties and biological in vitro activity.

(b) Comparability can be shown from a chemical-pharmaceutical perspective. During the whole comparability exercise, the same RMP should be used.

(2) In case the RMP has more than one indication, the efficacy and safety of the biosimilar medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications. Justification will depend on the clinical experience, the available literature data for the RBP, irrespective of the receptor(s) involved in all indications, the pre-clinical data, and the immunogenicity profile.

(3) Safety data will be needed prior to marketing authorization, as well as a Plan for Period Safety Update Report, as possible differences might become evident later, though comparability with regard to efficacy has been shown.

3.2 Issues Regarding Biological Activity (*In Vitro* and *In Vivo* Studies)

The combined results from in vitro and in vivo studies assist in the extrapolation of the findings to humans. (See ICH S6).

3.3 Issues Regarding Immunogenicity

Many biosimilars intended for human are immunogenic in animals. Therefore, measurement of antibodies associated with administration of these types of products should be performed when conducting repeated dose toxicity studies, in order to aid in the interpretation of these studies.

The detection of antibodies should not be the sole criterion for the early termination of a pre-clinical safety study or modification in the duration of the study design, unless the immune response neutralizes the pharmacological and/or toxicological effects of the biosimilar in a large proportion of the animals. In most cases, the immune response to biosimilars (and all biopharmaceuticals) is variable, like that observed in humans. If the interpretation of the data from the safety study is not compromised by these issues, then no special significance should be ascribed to the antibody response.

The induction of antibody formation in animals is not predictive of a potential for antibody formation in humans. Humans may develop serum antibodies against humanized proteins, and frequently the therapeutic response persists in their presence.

3.4 Issues Regarding Comparability

Two situations are indicated in which comparability becomes necessary:

(1) When a product is claimed to be similar to the RMP after the expiry of the data protection period (new application procedure).

(2) When a change is introduced in the manufacturing process of the biosimilar product (either before or after the granting of a marketing authorization [variation procedure]).

In either case the applicant will have to demonstrate or justify that the biosimilar product and RBP have similar profiles in terms of quality, safety and efficacy. This might be a sequential process, beginning with quality studies (partial or comprehensive) and supported, as necessary, by pre-clinical and/or clinical bridging studies to provide useful signals of potential therapeutic differences.

Chapter 4 : Clinical Studies

4.1 Introduction

The requirements for the clinical studies depend on the existing knowledge about the RBP and the claimed therapeutic indication(s). A comparability exercise must be conducted.

It is recommended to generate the required clinical data for the comparability study with the test product as produced with the final manufacturing process and, therefore, representing the quality profile of the batches to become commercialized. Any deviation from this recommendation should be justified and supported by adequate additional data.

4.2 Pharmacokinetic (PK) Studies

The PK profile is an essential part of the basic description of a medicinal product and should always be investigated. PK studies should generally be performed for the routes applied for and using doses within the therapeutic dose range recommended for the RBP.

PK studies must be comparative in nature and should be designed to enable detection of potential differences between the biosimilar and the chosen RBP.

4.3 Pharmacodynamic (PD) Studies

The pharmacodynamic effect should be compared in a population where the possible differences can best be observed. The design and duration of the studies must be justified. Pharmacodynamics should preferably be evaluated as part of the comparative

pharmacokinetic study, since alterations in pharmacodynamics can sometimes be explained by altered kinetics and such design may provide useful information on the relationship between exposure and effect.

The selected dose should be in the steep part of the dose-response curve. Studies at more than one dose level may be useful. Again, studies should be comparative in nature and not merely show the pharmacodynamics of the product.

General guidance for conducting clinical trials can be obtained from the Guidelines for Clinical Trials in Nigeria.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) website (www.ich.gov) provides more general considerations for clinical trials regarding the objectives, design, conduct, analysis and reporting.

4.4 Efficacy studies

Dose finding studies are not required for a biosimilar. Demonstration of comparable potency, PK and PD profiles provide the basis for the use of the posology of the RBP in the confirmatory clinical trial(s).

Similar efficacy of the biosimilar and the chosen RBP will usually have to be demonstrated in adequately powered, randomized, and controlled clinical trial(s). The principles of such trials are laid down in relevant ICH guidelines 8, 9.

In principle, equivalence designs (requiring lower and upper comparability margins) are clearly preferred for the comparison of efficacy and safety of the biosimilars with the

RBP. Non-inferiority designs (requiring only one margin) may be considered if appropriately justified.

Equivalence/ non-inferiority margins have to be pre-specified and justified based on clinical relevance; i.e. the selected margin should represent the largest difference in efficacy that would not matter in clinical practice. Treatment differences within this margin would thus, by definition, be acceptable because they have no clinical relevance.

Generally, equivalence trials are clearly preferable to ensure that the biosimilar is not clinically less or more effective than the RBP when used at the same dosage(s). For biosimilar with a wide safety margin, non-inferiority trials may also be acceptable. It should, however, be considered that non-inferior efficacy, by definition, does not exclude the possibility of superior efficacy of the biosimilar compared to the RBP which, if clinically relevant, would contradict the principle of similarity.

4.6 Immunogenicity

This is the most important aspect of safety of biosimilars. For many proteins and peptides, a number of patients develop clinically relevant anti-drug antibodies. The immune response against therapeutic proteins differs between products since the immunogenic potential is influenced by many factors.

For further information, please refer to ICH S8.

4.7 Risk Management and Pharmacovigilance

The applicant should give a risk specification in the application DMF for the biosimilars under review. This includes a description of possible safety issues related to tolerability of the product that may result from a manufacturing process different from that of the innovator. In the DMF, the applicant should present a Risk Management Plan and Period Safety Update Report (PSUR) in accordance with current NAFDAC procedures and guidelines. This should take into account risks identified during product development and potential risks. Pharmacovigilance systems and procedures to achieve this monitoring should be in place before a marketing authorization is granted. Any specific safety monitoring imposed to the RMP or product class should be taken into consideration in the risk management plan.

The compliance of the marketing authorization holder with commitments (where appropriate) and their pharmacovigilance obligations will be closely monitored. The marketing authorization holder should address reports and any other information on tolerability of the biosimilar that the company has received. These reports or information must be evaluated and assessed by the marketing authorization holder in a scientific manner with regard to causality of adverse events or adverse drug reactions and related frequencies.

For further information on this issue, ICH Q9 can be used. For reporting, NAFDAC Guidelines on Pharmacovigilance should be referred to.