Ongoing Development of Guidelines for Biosimilar Medicines Assessment in Uganda: Critical Evaluation and Recommendations for Inclusion

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TITLE

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Key words: Biosimilars, Medicines assessment in Africa; Registration of medicines in Uganda; non-communicable diseases

SUMMARY

Background:

A biosimilar is defined as a biologic product that is similar but not identical to the reference/originator biologic product. Biologic products have raised hopes of improving the quality of life especially in the treatment of chronic non-communicable diseases (NCDs). Of all the major health threats to emerge since the start of this century, none has challenged the very foundations of public health as profoundly as the rise of NCDs. However, the increasing cost of treatment of biologic products has raised many questions regarding its access in the context of multiple inequalities. The arrival of the patent cliff in this sector has given rise to biosimilars.

The emergence of biosimilars is expected to go a long way in reducing the cost of care of NCDs. The use of biosimilars is based on the assumption that they are of assured quality and of the same pharmaceutical standard as the reference biologicals. Their quality should therefore be rigorously controlled and assured. Uganda has had biologicals on its market that are claimed to be copies of the originator biologicals also known as biosimilars. Most of these products have not been approved through a biosimilar approval procedure, but have instead been licensed (by the Uganda National Drug Authority (NDA)) using the same requirements as generics or small molecule medicines. According to the World Health Organization (WHO) *Guidelines on the Evaluation of Similar Biotherapeutic Products*, a biosimilar that has not been demonstrated to be similar to a reference product through head-to-head comparisons should not be described as similar or be called a biosimilar. Although these products are on the Ugandan market, based on the above, they cannot be referred to as biosimilars. In November 2017 however, NDA embarked on the process of developing guidelines for assessment of biologics, and a specific guideline for assessment of biosimilars. The proposed title for the biosimilar assessment guidelines is; '*Guidelines for Registration of Similar Biotherapeutic products*.' The purpose of the

research was to assess whether the proposed guideline makes acceptable provision for internationally accepted standards of quality, safety and efficacy of biosimilars, and to make recommendations for inclusion based on internationally accepted practices.

Method:

The study employed the principles of explorative comprehensive literature-based review using a thematic qualitative approach. The method of data collection was documentation, collected and selected using document review and analysis. Documentation used for the research was obtained by internet search, using the google search engine. The method chosen was in keeping with the aims and objectives of the study to critically evaluate the proposed NDA biosimilar assessment guidelines by comparison of the proposed guidelines with those from chosen jurisdictions, i.e. European Union (EU), U.S.A, WHO and South Africa; and make recommendations for identified gaps.

Results:

The key scientific principles for establishing biosimilarity with respect to quality, non-clinical and clinical requirements, are the same across the chosen jurisdictions and in the proposed NDA biosimilar guidelines. They all require establishing biosimilarity using a stepwise approach. They require a comprehensive comparison of the quality attributes of the biosimilar and reference products. Fulfilment of this requirement then determines the need and amount of additional studies required i.e. non-clinical and clinical studies. A risk-based approach is used to evaluate all data and information in support of the biosimilarity of the proposed product. The depth of information included however varies, for example, the EU and U.S.A guidelines provide detailed information on the biosimilarity approach in comparison to the other jurisdictions. The types of studies at each step are specified in detail. In addition, the clinically meaningful differences that would lead to rejection of biosimilar applications are well defined.

Unlike the selected jurisdictions, NDA's position on reference product requirements, extrapolation of indications and interchangeability principles was not stated.

Inconsistencies were also found in some sections of the proposed NDA guideline. These were highlighted and recommendations provided, for example, inconsistencies were observed in the glossary of terms, inclusion of a Public Assessment Summary Information for Similar Biotherapeutic Product and not a Summary Information for Similar Biotherapeutic Product as mentioned in the guideline among others. Some of the recommendations for inclusion based on standards from the chosen jurisdictions are included; information on reference product sourcing applicable to Uganda, NDA's position on interchangeability and/or substitution; and on possibility of extrapolation of efficacy and safety from one indication to another.

Conclusion:

Availability of biosimilar assessment guidelines will go a long way in ensuring that NDA effectively regulates biosimilars to ensure that only safe, efficacious and good quality biosimilars are available on the Ugandan market, and increase confidence in these products. The proposed assessment guidelines are comparable with those from the selected jurisdictions with respect to the key technical assessment principles. These should therefore be finalized with recommended revisions and made available, for example, on the NDA website. The recommendations as attached in Appendix I, were shared with NDA.

DECLARATION

I declare that this thesis that I now submit for assessment on the programme of study leading to the award of Master of Science in Pharmacy Administration and Policy Regulation has not been submitted as an exercise for a degree at this or any higher education institution. It is entirely my own work and has not been taken from the work of others, save the extent that such work has been cited and acknowledged within the text of my work.

I agree to deposit this thesis in Hibernia College's institutional repository and the University of Western Cape's or allow the library to do so on my behalf, subject to Irish and South African Copyright Legislation and Hibernia College Libraries and the University of the Western Cape's conditions of use and acknowledgement.

Signature:

Date: 13 February 2020

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LIST OF ABBREVIATIONS

DNA	Deoxyribonucleic acid
EAC	East African Community
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MAA	Marketing Authorization Application
MCC	Medicines Control Council
NCDs	Non Communicable Diseases
NDA	National Drug Authority (Uganda)
NRA	National Regulatory Authority/Agency
PRCA	Pure red cell aplasia
RBP	Reference Biotherapeutic Product
RMP	Risk Management Plan
SA	South Africa
SAHPRA	South African Health Products Regulatory Authority
SBPs	Similar Biotherapeutic Products
USA	United States of America
USD	United States Dollar
U.S. FDA	United States Food and Drug Administration

WHO	World Health Organization

Chapter One: Introduction

Of all the major health threats to emerge since the start of this century, none has challenged the very foundations of public health as profoundly as the rise of chronic Non Communicable Diseases (NCDs). The prevalence of heart disease, cancer, diabetes, and chronic respiratory diseases, once considered the close companions of affluent societies, is now global, with the heaviest burden concentrated in low-and middle-income countries[1]. According to the World Health Organization (WHO), 80% of deaths from NCDs now occur in low-and middle-income countries, up from 40% in 1990. By 2030, NCDs will be the leading cause of death and disability in every region in the world[2]. In fact, at the seventy-first World Health Assembly meeting held on 24 May 2018, Health Assembly delegates called for stepped up action in the global fight to eradicate NCDs, including urging for participation by heads of state and government at the Third United Nations General Assembly High-level Meeting on the Prevention and Control of NCDs held on 27 September 2018.

The advent of biologic therapeutic agents more than a decade ago has transformed the treatment of NCDs. Despite the benefits of these biologic therapies for treatment of these conditions however, not all patients for whom they are indicated receive them mainly because of the high purchase costs involved[3]. Annual costs of many biologics approach or exceed USD100,000, with some up to 22 times more expensive than small-molecule drugs[4]. However, patents of many biologic medicines have already expired or will soon reach their expiry date. This has led to increased interest in the development of biosimilars, which are similar to the original biologic agents. According to a country-wise biosimilar pipelines number in development worldwide carried out in 2017, China had 269 biosimilars in development, which was the largest number, followed by India with 257 biosimilars in development. Other countries included USA (187), South Korea (109), Russia (97), Switzerland (57), Argentina (48), Japan (45) and Brazil (37)[5]. The development of biosimilars after the expiry of patents of the original products is expected to make biologics available at more affordable prices and to increase their use by

providing more treatment options[6]. In the United States of America (U.S.A), five-year cost savings of USD256 million are estimated with use of filgrastim biosimilar[7].

However, unless their quality, efficacy and safety are assured, biosimilars like any other biologics can present with unknown or dire consequences to public health2. As mentioned above, there are several biosimilars under development worldwide. However, some of the countries from which the biosimilars are developed do not have stringent regulatory agencies. In several African countries including Uganda, lack of relevant competencies for regulation of biologicals and biosimilars resulted in issuance of marketing authorization for biosimilars using criteria for generic medicines[2]. The lack of appropriate regulatory framework has in turn restricted market access to biosimilars. Only few health care providers are aware of biosimilars presence in the market. This is attributed to the lack of confidence in efficacy, safety and manufacturing process of the biosimilars[6, 8].

Improving access to biosimilars and ensuring they are used appropriately requires a high degree of collaboration between various stakeholders, each of which has a distinct role. The main roles of regulatory authorities, such as, National Drug Authority (NDA), for example, are to provide regulatory oversight of biosimilars throughout their product life-cycle and to ensure that only high-quality; safe and efficacious biosimilars are available on the market [6]. Like other therapeutic products, biosimilars require effective regulatory oversight for the management of the potential risks they pose and to maximize their benefits9.

Uganda's NDA embarked on the process of developing guidelines for assessment of biologics, and a specific guideline for assessment of biosimilars, in November 2017. The proposed title for the biosimilar assessment guidelines is; '*Guidelines for Registration of Similar Biotherapeutic products*.' This is the subject matter for this research. At the time of the research, the guideline had not yet been finalized.

The purpose of this research therefore was to assess the current work done in this regard (Current draft – May 2018), and make recommendations based on internationally accepted practices from European Medicines Agency (EMA), the United States Food and Drugs Administration (US FDA), the World Health Organization (WHO), and the South African Health Products Regulatory Authority (SAHPRA), guidelines for biosimilars, and also on best practices come across during literature review.

Chapter Two: Literature Review

2.1 Biosimilars

Biosimilars are biologic products that are similar but not identical to reference/originator biologic products. Although described differently by various global health agencies, biosimilars generally are large-molecular-weight, complex molecules that are produced in living cells through genetic engineering[10]. Biologics differ from conventional small molecule drugs in that they are created from living organisms, either naturally or via genetic manipulation (e.g. monoclonal antibodies) or are manufactured from complex building blocks of living organisms (e.g. siRNA, aptamers,). In either case, they demonstrate considerable molecular complexity and heterogeneity, and are more difficult to characterize physico-chemically than synthetic chemical entities. Indeed, some components of a finished biologic may be unknown. These large, complex molecules, or mixtures of molecules, are often manufactured using recombinant DNA technology. Examples include insulin, growth hormones and erthropoietins[11]. This complexity means that for biologics, the product is the process, and manufacturers must use a manufacturing process that remains consistent over time to ensure product consistency, quality and purity [11].

In contrast, conventional drugs, chemical entities of low molecular weight typically ranging from 300 to 600 daltons, are typically produced by chemical synthesis, have well-defined chemical structures and can be analysed to identify all components. Drug makers can alter the production process extensively and use laboratory test to confirm that the product remains the same[11]. These differences are reflected when branded products are substituted with generics, once patent life has expired, a step that has contributed enormously to making many medicines affordable.

For biologics, demonstration of comparability between different forms of a biological product is very demanding because the products cannot be identical, only similar, hence the term 'biosimilar' [11].

Table 2.1: Summary of key differences between biosimilars and generics[10, 11]

Biosimilars	Generics
While the primary amino acid backbone of a biosimilar protein is identical to that of the reference product, the glycosylation pattern will vary with the cell type used, and its activity including immunogenicity.	Active substance is similar to the reference and is generally administered at the same dose to treat the same disease
Complexity of production makes exact replication of the originator molecule virtually unattainable with batch-to batch variation	Same qualitative and quantitative composition with respect to active substances as innovator product
A stepwise approach is used to demonstrate biosimilarity between the reference product and biosimilar. The stepwise demonstration of biosimilarity includes *in vitro* analytical testing, nonclinical comparative pharmacology, toxicology, pharmacokinetic (PK) testing, and one or more clinical trials to confirm quality, efficacy, and safety of the proposed biosimilar as compared with the reference product[69].	A direct comparison of the reference product and generic medicine is required to claim equivalence. Comparison is usually made by an *in vivo* PK study in humans showing that the rate of absorption and extent of bioavailability lie within strictly defined limits. This is referred to as a bioequivalence study or therapeutic equivalence study. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.
20-30 % discount over reference product	80-90 % discount over reference product
$*100 - $200M in development costs	$1 - $5M in development costs
8 – 10 year development timeline	3 – 5 year development timeline
No interchangeability or automatic substitution. Scientific justification has to be provided	Interchangeable with reference product without justification

*$ is the currency symbol for United States Dollar (USD).

2.2 Background to regulation of biosimilars

Historically, the European regulatory authority, the EMA has taken a global leadership role on biosimilar drug development and approval. The WHO and a number of developed and other developing nations followed the EMA's lead by adopting similar principles in their guidelines. Examples of onset of biosimilar regulation in different markets were as follows: South Africa (2009), Japan (2009), WHO (2010), Canada (2010), USA (2010), New Zealand (2011) and India (2012)[12].

An initial unfortunate experience with a biosimilar product in the late 1990s served as an alert to the inherent risks of making apparently small changes to a biological product[11,13]. Hospira's biosimilar epoetin zeta (Retacrit®), was approved by EMA to the reference biologic Eprex® (Amgen/Johnson & Johnson), a synthetic erythropoietin (epoetin alpha) used to replace the erythropoietin that is deficient in renal failure patients who cannot make enough erythropoietin, and to treat cancer patients developing anaemia because of chemotherapy treatment. Whilst preapproval nonclinical *in vivo* physicochemical studies proved epoetin zeta to be biosimilar to Eprex®, clinical trials showed low potency, depicting differences in the proteins that are discerned with the available technologies. An unforeseen burst of pure red cell aplasia (PRCA) occurred in patients with anaemia of renal failure treated with Eprex® in 1998. In order to comply with EMA's request, to minimize the risk of serious infections with proteins of human origin, the company replaced human serum albumin (HSA) with polysorbate 80 and glycine as stabilizers. The new formulation resulted in the development of antibodies that neutralized both the recombinant protein and the native hormone leading to an increase in the frequency of cases with PRCA, requiring some patients to have blood transfusions and dialysis. The cause of the pure red cell aplasia did not become apparent for some time. Eventually, it was established that the polysorbate 80 leached from uncoated rubber bungs in prefilled syringes for subcutaneous injection and behaved as an adjuvant, resulting in a greatly enhanced immune reaction to the epoietin alpha. Subsequently, the problem was resolved by replacement of the rubber bungs in the prefilled syringes with fluoro-resin coated stoppers [11,13].

It is believed, that this statutory lesson perhaps contributed to the rigorous approach of the EMA to establishing the similarity of both structure and activity of biosimilars to that the reference product, and also for the world to look at biologics and more specifically biosimilars with caution[11,13].

The goal of the regulatory agencies is to ensure that biosimilars meet high standards of quality, safety, and efficacy, and are highly similar to the reference product. However, although there are many regulatory guidance documents, there is so far no global consensus on the regulatory pathway for biosimilars. Many countries, besides the USA and the European Union (EU), are currently authoring guidance documents for biosimilars. Several, including Canada, Brazil, South Africa, Japan, and Korea have used the principles for establishing biosimilarity outlined in the WHO guidance documents as a platform for authoring their national guidelines (Figure 2.1) [14]

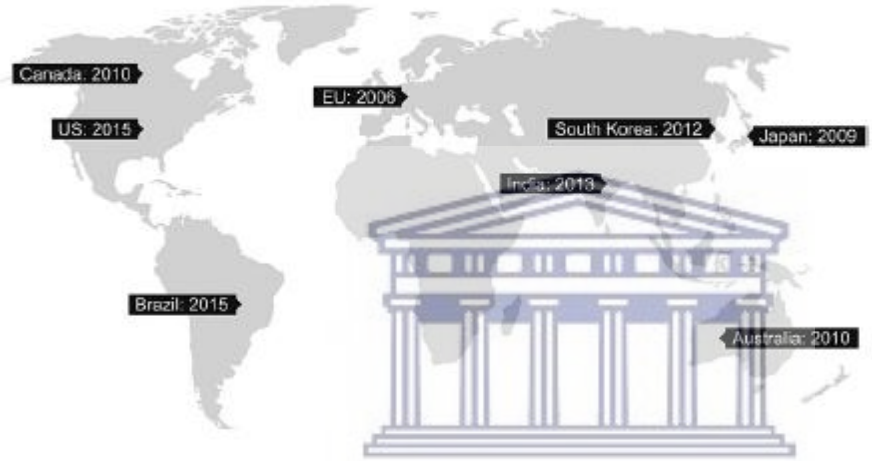

Figure 2.1: Evolution of the biosimilars regulatory landscape across the globe.

2.3. Overview of biosimilar regulation in chosen jurisdictions

Biosimilar regulation in the chosen jurisdictions; EU, South Africa, U.S.A, WHO and Uganda is discussed in more detail in the following sections. The rationale for selection of the chosen jurisdictions is provided in the Work Plan (Chapter 3). Information was obtained from the websites of the respective agencies responsible for regulation of biosimilars, as applicable. The following information was provided for each of the regulatory agencies; responsible agency, regulatory framework, available biosimilar guidelines, patent information for reference biotherapeutic products and availability of multi-stakeholder information (access to biosimilar information).

2.3.1. Biosimilar regulation in the EU

EMA is responsible for evaluating most of applications to market biosimilars in the EU15. As earlier mentioned, the EU through EMA pioneered the regulation of biosimilar medicines with the first biosimilar (Omnitrope® - biosimilar recombinant human growth hormone [rhGH]; manufactured by Sandoz, Kundl, Austria), approved in 2006[15,16]. Omnitrope® is used to treat growth failure in children and adults who lack natural growth hormone, and in those with chronic kidney failure, Noonan syndrome, Turner syndrome, short stature at birth with no catch-up growth, and other causes[17]. EMA has acquired over ten years of experience in biosimilars regulation[15, 16].

In the EU, biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines. Marketing authorization is granted in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended. Specific to biosimilars, the legal basis of Article 10(4) of Directive 2001/83/EC and Section 4, Part II, Annex I to the said Directive lays down the requirements for the Marketing Authorization Applications (MAAs) based on the demonstration of the similar nature of the two biological medicinal products[15].

Biosimilars can only be authorized once the patent on the reference biological medicine has expired. According to the website, the biological reference medicine must have been authorized for at least eight years before another company can apply for approval of a similar biological medicine[15].

Information on biosimilars is readily available on the EMA website. EMA has not only published guidance and guidelines for biosimilar manufacturers/developers, but has also published information for patients and health care professionals to improve understanding of biosimilar medicines in the EU. The following information for patients and health care professionals is currently published[15]:

- An animated video for patients explaining key facts on biosimilar medicines and how EMA works to ensure that they are safe and effective as their reference biological medicines. The video is currently available in the following European languages: Dutch, English, French, German, Italian, Polish, Portuguese and Spanish.

- An information guide for patients published by the European Commission explaining what biosimilar medicines are, how they are developed and approved in the EU and what patients can expect in terms of availability and safety. The guide is available in 23 official EU languages.
- Biosimilars in the EU – Information guide for health care professionals. The guide is available in eight (8) languages; English, Dutch, French, German, Italian, Polish, Portuguese and Spanish.

In addition, the EU publishes summaries of the European public assessment reports (EPARs) for each of the approved biosimilars. The reports explain how EMA assessed the medicine to recommend its authorization in the EU and its conditions of use. Product information which provides practical information for health care providers and patients is also published for each approved biosimilar. The product information includes summary of product characteristics, labelling information and package insert or patient information leaflet (PIL) [15].

The EU follows a multidisciplinary approach for biosimilar regulation18. The Committee for Medicinal Products for Human Use (CHMP) issues specific guidelines concerning scientific data to be provided to substantiate the claim of similarity used as the basis for a MAA for any biological medicinal product. Listed below are the scientific guidelines currently published by EMA that assist medicine developers to prepare marketing authorization applications for biosimilars 18:

Overarching biosimilar guidelines*:

1. Similar biological medicinal products – outlines the general principles to be applied for similar biological medicinal products
2. Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues
3. Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues

Product-specific biosimilar guidelines:

1. Biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor (Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues)

2. Non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins
3. Non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues
4. Similar biological medicinal products containing interferon beta
5. Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues
6. Similar biological medicinal products containing recombinant erythropoietins
7. Similar biological medicinal products containing recombinant follicle-stimulating hormone
8. Similar medicinal products containing somatropin (Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues)

Other guidelines relevant for biosimilars:

1. Comparability of biotechnology-derived medicinal products after a change in the manufacturing process - non-clinical and clinical issues
2. ICH Q5E Biotechnological/biological products subject to changes in their manufacturing process: comparability of biotechnological/biological products
3. Immunogenicity assessment of biotechnology-derived therapeutic proteins
4. Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use

**Only the overarching biosimilar guidelines were considered and reviewed for this project.*

According to the website, 59 biosimilars have currently been approved by EMA. Information on approved products including public assessment reports is available at the following website; https://www.ema.europa.eu/en/search/search/search_api_aggregation_ema_medicine_types/field_ema_med_biosimilar?search_api_views_fulltext=biosimilars%20approved%20by%20EU

2.3.2 Biosimilar regulation in the USA

In the USA, biosimilars are regulated by the U.S. Food and Drug Administration (FDA)'s Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER)19.

The FDA approved its first biosimilar, Zarxio® (filgrastim, a recombinant, non-pegylated human granulocyte colony stimulating factor [G-CSFT] manufactured by Sandoz) in March 2015. It is used to treat low blood neutrophils in the immune compromised, for example in AIDs patients, following chemotherapy or radiation poisoning[20].

Marketing authorization for biosimilars is granted in accordance with the provisions of section 351 (k) of the Public Health Service Act (PHS Act). The Biologics Price Competition and Innovation Act of 2009 (BPCI) was enacted as part of the Patient Protection and Affordable Care Act (Affordable Care Act) (Public Law 111-148) on 23 March 2010. The BPCI Act amends the PHS Act and other statutes to create an abbreviated licensure pathway in section 351(k) of the PHS Act for biological products shown to be biosimilar to or interchangeable with an FDA-licensed biological reference product (sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Affordable Care Act)[19].

Section 351(k) of the PHS Act, entitled "Exclusivity for Reference Product," has the following provisions; "approval of a 351(k) application may not be made effective until 12 years after the date of first licensure of the reference product (statute excludes the date of licensure of supplements and certain applications); A 351(k) application for a biosimilar or interchangeable biological product cannot be submitted for review until 4 years after the date on which the reference product was first licensed under section 351(a) of the PHS Act." As provided by section 351(m) of the PHS Act, an additional six-month period of exclusivity (in which a biosimilar or interchangeable biological product cannot be licensed or accepted for review) will attach to the 12- and 4-year periods, respectively, if the sponsor conducts pediatric studies that meet the requirements for pediatric exclusivity pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Furthermore, a biological product seeking licensure as biosimilar to or interchangeable with a reference product indicated for a rare disease or condition and granted 7 years of "orphan drug exclusivity" under section 527(a) of the FD&C Act, may not be licensed by FDA for the protected orphan indication until after the expiration of the 7-year orphan drug exclusivity period or the 12-year reference product exclusivity period granted under section 351(k)(7) of the PHS Act, whichever is later [19].

Information on biosimilars is readily available on the U.S.FDA website[19]. In addition to the various guidances listed below, U.S.FDA published a Biosimilars Action Plan (BAP) to provide information

about the key actions the agency is taking to encourage innovation and competition among biologics and the development of biosimilars. Also, through its Center of Drug Evaluation and Research (CDER), the FDA offers a variety of patient and prescriber outreach materials including: videos [The Promise of Biosimilars, The Basics of Biosimilars, The Concept of Interchangeability, The Biosimilar Development Process, and Analytical Data for Biosimilar Products]; Fact sheets [Biological Product Definitions, Biosimilar Product Regulatory Review and Approval, Prescribing Biosimilar Products, and Prescribing Interchangeable Products]; Infographics [Biosimilar Development Process, and What is a Biosimilar]; and stakeholder toolkit intended to help stakeholders promote FDA as a resource for information on biosimilars and interchangeable products and to encourage prescribers and patients to talk to each other about these medicines. The stakeholder kit includes: animated GIFs, website badges, print Ads, infocards, twitter posts and facebook/LinkedIn posts.

The website also includes drop-in content e.g. newsletter articles for prescribers and patients related to biosimilars. In addition to the above, the FDA offers online courses, webinars and presentations (FDA staff presentations) to help manufactures, the public and regulators worldwide learn more about biologics, biosimilars and interchangeable products. Product information, that is, prescribing information and any other related information e.g. press releases is available for each of the approved biosimilar medicines[19].

Below are the scientific guidelines currently published by U.S.FDA intended to help medicine developers prepare marketing authorization applications for biosimilars19:

1. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product ; final (2015)**
2. Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; final (2015)**
3. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, final (2016)**
4. Reference Product Exclusivity for Biological Products Filed Under; draft (2014)
5. New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2); draft (2018)
6. Questions and Answers on Biosimilar Development and the BPCI Act, final (2018)
7. Considerations in Demonstrating Interchangeability With a Reference Product Guidance for Industry, draft (2017)

8. Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products Guidance for Industry, draft (2018)

***These guidelines were considered and reviewed for the project.*

Table 2.2: U.S.FDA has currently approved 17 biosimilars as shown in the list below[19, 21]

Product Name	Approval Date
Zarxio (filgrastim-sndz)	March 2015
Inflectra (infliximab-dyyb)	April 2016
Erelzi (etanercept-szzs)	August 2016
Amjevita (adalimumab -atto)	September 2016
Renflexis (infliximab-abda)	May 2017
Cyltezo (adalimumab-adbm)	August 2017
Mvasi (bevacizumab-awwb)	September 2017
Ogivri (trastuzumab-dkst)	December 2017
Ixifi (infliximab-qbtx)	December 2017
Retacrit (epoetin alfa-epbx)	May 2018
Fulphila (pegfilgrastim-jmdb)	June 2018
Nivestym (filgrastim-aafi)	July 2018
Hyrimoz (adalimumab-adaz)	October 2018
Udenyca (pegfilgrastim-cbqv)	November 2018
Truxima (rituximab-abbs)	November 2018
Herzuma (trastuzumab-pkrb)	December 2018
Ontruzant (trastuzumab-dttb)	January 2019

2.3.3 Biosimilar regulation by the WHO

The WHO is not a drug regulatory agency although it has unique regulatory roles. One of WHO's mandates is to aid member states to strengthen regulation, including post-marketing surveillance, and to eliminate substandard and falsified medicines[22]. In as far as regulation is concerned, WHO currently has the following roles listed below for ease of reference22;

- Developing international norms, standards and guidelines to ensure that countries worldwide can regulate health products and technologies consistently. Norms, guidelines and standards

have been developed for biologicals including biosimilars, blood products, International Nonproprietary Names (INNs), Quality assurance including of medicinal products, and immunization standards

- Regulatory system strengthening (RSS). RSS helps member states through a variety of approaches including: assessment of regulatory functions using a standardized tool*** and the creation of an institutional development plan (IDP) designed to bring each NRA up to benchmarked international standards; direct technical assistance based on country IDPs; and support for information and work-sharing arrangements made possible through the implementation of harmonized standards and best practices and the creation of regional and global regulatory networks (WHO collaborative procedure).

****The WHO Global Benchmarking Tool (GBT) helps measure national regulatory systems against defined indicators in order to identify areas for improvement in the form of IDPs. A key objective of the benchmarking process is to help regulatory authorities, particularly those in low- and middle-income countries, reach a level of maturity commensurate with a stable well-functioning and integrated system of oversight for medical products (Maturity Level 3).*

- Promoting global safety of medical products by coordinating global networks for information sharing, such as data bases and monitoring and alert systems, and by supporting countries to develop national capacities for the post-marketing surveillance of health products.
- Prequalification of medicines[23]. The WHO Prequalification Team (WHO PQT) was formed with the aim of guiding UN agencies and other international organizations with respect to the quality of antiretroviral medicines, for supply to low-income countries. Currently, its services cover assessment for a range of finished pharmaceutical products (FPP), in several therapeutic areas: HIV/AIDS, tuberculosis, malaria, hepatitis (B & C), diarrhoea (specifically zinc products), neglected tropical diseases, influenzae and reproductive health conditions) and assessment of active pharmaceutical ingredients (API). It carries out inspection of FPP, API, clinical sites and quality control laboratories. It also provides technical assistance, and conducts extensive training activities.

  According to the WHO website24, in order to explore options to facilitate access to safe, effective and quality assured biotherapeutics and biosimilars, the WHO on 05 July 2018 launched a pilot project to prequalify selected biologics and biosimilars, as a step forward to support national and global efforts to increase access to and the affordability of these products. This followed the World Health Assembly (WHA) adoption of Resolution WHA67.21 on "*Access to biotherapeutic products, including biotherapeutic products (biosimilars), and*

ensuring their quality, safety and efficacy". Like the Prequalification of medicines program which was established in 200125, the pilot project is aimed at working in close cooperation with national regulatory agencies and partner organizations to make quality priority biotherapeutics and biosimilars available for those who urgently need them.

WHO has currently invited manufacturers to submit applications for prequalification of two biotherapeutic products in the WHO Essential Medicines List: rituximab (used principally to treat non-Hodgkin's lymphoma and chronic lymphocytic leukaemia), and trastuzumab (used to treat breast cancer) and their corresponding similar biotherapeutic products.

In 2009, the WHO issued its first guidance, *the Guidelines on evaluation of similar Biotherapeutic Products (SBPs), Annex 2, Technical Report Series No. 977, 2009*. It has since issued additional publications related to biosimilars, intended to give guidance to manufacturers and medicine regulators. Listed below is the list of available guidances[22,23];

- 1st invitation for expression of interest to manufacturers of biotherapeutic products and biosimilars
- WHO pilot procedure for prequalification of biotherapeutic products: rituximab and trastuzumab
- WHO guidelines on submission of documentation for the pilot procedure for prequalification of similar biotherapeutic products for rituximab and trastuzumab. Preparation of product dossiers in common technical document format – Full Assessment****
- WHO guidelines on submission of documentation for the pilot procedure for prequalification of rituximab and trastuzumab approved by stringent regulatory authorities (SRA) – Abridged assessment
- Quality Information Summary (QIS) of the biotherapeutic product approved by SRA.
- Guidelines on evaluation of similar Biotherapeutic Products (SBPs), Annex 2, Technical Report Series No. 977, 2009****
- Post ECBS 2018 - WHO Questions and Answers: Similar Biotherapeutic Products
- Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 1004, 2016

**** *These guidelines were considered and reviewed for this research project.*

2.3.4. Biosimilar regulation in South Africa

Biosimilars in South Africa are regulated by the South African Health Products Regulatory Authority (SAHPRA), formerly known as the Medicines Control Council (MCC)[26]. According to the information in the guidelines, marketing authorization of biosimilars is granted based on the provisions in the Medicines and Related Substance Act, 1965 (Act 101 of 1965), as amended and the relevant regulations 26.

Until 2018, there were no statutory provisions in South African patent law or medicines regulatory laws dealing specifically with data exclusivity. There were however provisions in the medicines regulatory law, and other legislation, which deal with the protection of confidential (such as trade secret) information27. However, in 2018 the South African government adopted the Intellectual Property Policy which gives effect to the 2001 Doha Declaration on the TRIPS (Trade-Related Aspects of Intellectual Property Rights). The policy is expected to lay the groundwork for regulations to be put in place and laws to be passed to give effect to intellectual property reform in South Africa28,29. There is currently no exclusivity period requirement for reference products by SAHPRA.

According to the SAHPRA website, the available guideline is the 2014 Biosimilar medicines quality, non-clinical and clinical requirements[26]. It is intended to provide recommendations to applicants wishing to submit applications for the registration of biosimilar medicines26. Information on approved biosimilars was not available on the SAHPRA website.

2.3.5 Biosimilar regulation in Uganda

Biosimilars in Uganda are regulated by the NDA[30].

According to the information in the proposed guidelines, marketing authorization for biosimilars in Uganda is granted in accordance with the provisions of sections 35(1)(a) and 35(3) of the National Drug Policy and Authority Act Cap 206[30]. Currently, Uganda has no guidelines for biosimilars. The proposed

guidelines; *Guidelines for Registration of Similar Biotherapeutic Products*, May 2018 are yet to be finalized. These are the subject of this research and have been attached as appendix III.

Currently, there are no statutory provisions in Uganda patent law or medicines regulatory laws dealing specifically with data exclusivity of medicinal products. Although Uganda signed the TRIPS agreement with the World Trade Organization (WTO) in 1995, it has not incorporated the flexibilities and safeguards into national law. A respective amendment was drafted in 2004 but has not yet been approved by the Ugandan Parliament[31].

There is currently no information on biosimilars on the NDA website. A separate list of approved biosimilars is also not available. Biosimilars and biological medicines are listed along with other medicine categories including generics in the human drug register published on the website. It is updated on a monthly basis. From the register, it is not possible to filter out biosimilars since there is neither provision for therapeutic class or group or pharmacological/biotechnology classification. However, the list of currently approved/registered biosimilars was requested for and obtained from NDA's Product Assessment and Registration (PAR) department via email, a copy of which was included in Appendix II. Currently 30 biosimilars are registered by NDA as per the Table 2.3.

Table 2.3: List of biosimilars registered in Uganda as of 02 February 2019

Product Name	Year of registration
Repoitin Injection 2000, Recombinant Human Erythropoietin (rHuEPO)	2012
Insugen R [Regular], Human Insulin	2012
Insugen N [N.P.H], Human Insulin	2012
Insugen -30/70, Human Insulin	2012
Repoitin Injection 2000, (rHuEPO)	2013
Heparin, unfractionated heparin (UFH)	2014
Insuman Comb 30, Human Insulin	2014
Levemir Flexpen 100u/ml, Human Insulin	2014
Novomix 30 Flexpen, Human Insulin	2014
NovoRapid Flexpen, Human Insulin	2014
Lomoh -80, Enoxaparin sodium	2014
Isuman Rapid 100IU/ml, Human Insulin	2015

Gonal-F 300 IU, Follitropin alfa, 300 IU/0,5 ml (22 µg/0,5 ml)	2015
Gonal-F 450 IU, Follitropin alfa, 450 IU/0,75 ml (33 µg/0,75 ml)	2015
Gonal- F 900 IU, Follitropin alfa, 900 IU/1,5 ml (66 µg/1,5 ml)	2015
Gonal -75 IU, Follitropin alfa, 75 iu (5.5 µg)	2016
Foligraf 75 I.U, Follicle stimulating hormone	2016
Lioton Gel, UFH	2016
Endulin Vial™, Insulin Glargine 100 IU/ Ml	2016
Endulin Vial™_ 1 vial of 3 ml, Insulin Glargine 100 IU/ Ml	2016
Endulin Cart™_3 mL cartridge, Insulin Glargine 100 IU/ Ml	2016
HuCoG-5000 HP, Chorionic gonadotrophin	2017
U-TRYP 100,000 I.U., Ulinastatin	2017
Lantus SOLOSTAR in a 3ml cartridge, Insulin Glargine	2017
Lantus solution for injection, 10ml vial, Insulin Glargine	2017
Lantus Solostar, Insulin Glargine	2017

2.4 Comparison of biosimilar guidelines

Sharma et al (2015) [12] provided an overview on the onset of biosimilar regulation in different markets with EMA having drafted its first set of guidelines in 2005. According to the publication, the WHO and a number of developed and other developing nations followed the EMA's lead by adopting similar principles in their guidelines. Examples of onset of biosimilar regulation in different markets were as follows: South Africa (2009), Japan (2009), WHO (2010), Canada (2010), USA (2010), New Zealand (2011) and India (2012). At the time of publication, Russia and China neither had specific regulations nor guidelines. Additionally, it was found out that the following countries regulated biosimilars in the same way as they did new biological products: Philippines, Taiwan, Indonesia and Thailand.

A presentation by Dr. Kamali Chance made at the Third International Conference and Exhibition on Biowavers, Biologics and Biosimilars, that lasted from October 27-29, 2014, in Hyderabad, India32 focused on comparison of EU (EMA) and US (US FDA) guidelines. According to the presentation, it was concluded that both guidelines shared similarities with respect to requirements for the reference product(s), a step-wise development approach i.e. each step of development should demonstrate acceptable similarity before proceeding to the next and need for a pharmacovigilance plan. It was concluded that both guidelines employ a risk-based approach in biosimilar product approval. However,

it was noted that the guidelines differed in their requirement for interchangeability, transition study, paediatric study assessment, and had different exclusivity periods for innovator biologics and for the first interchangeable product. For example, the US FDA provides for interchanging or substitution of the biosimilar and reference product without the intervention of the health care provider who prescribed the reference product, provided satisfactory justification is submitted. EMA however does not determine interchangeability or subsititution. The decision is left to the EU member states; The US FDA biosimilar guidances provided for paediatric study assessment whereas the EMA guidances did not.

Kirchoff CF et al (2017)14 discussed the challenges faced by pharmaceutical companies in the development of biosimilars. However, the publication also compared in detail EU EMA, US FDA and WHO requirements for selection of reference products, manufacturing requirement of biosimilars, the role of comparative *in vivo* non-clinical studies and scientific principles of extrapolation across indications.

Under manufacturing, both EMA and FDA allowed for advancements in formulation science to be incorporated in the biosimilar presentation i.e., the formulation excipients in the biosimilar may differ from those of the reference product, and, assessments are undertaken to elucidate any relevant effects of the revised formulation on the stability, physicochemical and functional characteristics of biosimilars[14].

On the role of comparative *in vivo* non clinical studies, although the global guidelines on biosimilar development were largely aligned in terms of the analytical and clinical aspects, there was substantial variability in the amount and type of *in vivo* nonclinical data required, with the EMA guidelines recommending minimal to no use of *in vivo* assays whereas other countries, such as Japan and China, Canada, required more extensive toxicity studies[14].

On the scientific principles of extrapolation across indications, although the decision to extrapolate data from one indication to another was made on a case-by-case basis, with strong scientific justification, based on the totality of evidence; the concepts were supported by the EMA and the USFDA regulatory guidelines[14].

IIiach et al (2017)33 focused on the current biosimilars landscape and discussed how the biosimilars pipeline was impacted by regulatory requirements in Canada, EU and the U.S. The discussion focused on comparison of the following within the three (3) jurisdictions: current biosimilar landscape, biosimilars development, and current uncertainties in regulatory requirements.

According to the publication, as earlier mentioned, the EU was leading the way with the largest number of regulatory approvals and the most extensive regulatory guidance, followed by Canada and, lastly the U.S. The following were identified as factors that could have led to delays in more approvals in these regions: capital required to conduct biosimilar trials, innovative strategies to delay the acceptance of biosimilars, litigation (especially in the U.S.), and lack of regulatory guidance around substitution33. Another key factor that was identified as requiring greater clarity was the acceptance of reference products from different jurisdictions, and harmonization of the approach on interchangeability [33].

According to the Derbyshire (2014) article34, a detailed comparison of biosimilar guidelines issued in Canada, the EU, Japan and Korea, and by the WHO was provided. In the article, the author noted that the clarity of the various guidelines is variable and the regulatory pathways were diverse, with agreement on how to define biosimilars differing sometimes significantly between different countries and regions. The author therefore recommended harmonization of regulatory standards for biosimilars would be of great advantage to biosimilar manufacturers. This would enable them to reduce costs and create a level playing field for manufacturers from different countries/regions. The development of a global reference product would also be of great advantage, as this would allow manufacturers to reduce the number of trials required for global approval [34].

2.5 Challenges in regulation of biosimilars

A presentation made by Hudu Mogtari2 in Cape Town, South Africa at the 17th International Conference on Drug Regulatory Authorities (ICDRA) that lasted from 27 November to 02 December 2016, highlighted that several African countries lack relevant competencies including specific guidance's for regulation of biologicals and biosimilars. This has resulted in issuance of marketing authorization for biosimilars using criteria for generic medicines, inability to conduct pharmacovigilance hence missing important signals, inability to carry out relevant post market surveillance (PMS) and Good manufacturing/handling practices inspections, treating large molecules (biologics) like small molecules (drugs) and ignoring the potential hazards of biosimilars. The issues raised by Mogtari (2016) were further highlighted by Kang et al (2018)35.The article which focused on the discussion of factors that give rise to barriers to market access for biosimilars; and explained the role of regulators and the importance of regulatory oversight throughout the product life-cycle of biosimilars; noted that some countries have biotherepautics on their markets that are claimed to be copies of original

products (i.e.so-called non-innovator or copy-version products). These medicines have not been approved through a biosimilar approval procedure but have, instead, been licensed as generics or small-molecule medicines. As stated in WHO's guidelines on the evaluation of similar biotherapeutic products, a biosimilar that has not been demonstrated to be similar to a reference product through head-to-head comparisons with a reference biotherapeutic product should not be described as similar or be called a biosimilar. Such products could be licensed using more extensive nonclinical and clinical data sets or full licensing applications35.

In other countries e.g. Lebanon, only drafts of regulatory guidelines for registration of biosimilars are available[8]. The publication *Review and results about biosimilars prescription and challenges in the Middle East and North Africa region*[8] attributes this lack of clear regulation to the fact that only a few physicians or health care providers are aware of biosimilars presence and as such hardly prescribe them in Lebanon and in the Arab region.

H.Sharma et al (2015)[12] highlighted challenges in the regulation of biosimilars in regions with established biosimilars regulation guidelines as mentioned under 2.4: differences in legal framework in different countries; lack of consensus across regions on acceptable pathway and parameters if the reference product is sourced outside own region; likely differences in the approved formulation and/or presentations of the reference product(s) internationally; lack of comprehensive guidance and consensus on the application of the most sensitive disease model (in testing of biosimilars) with respect to an indication not globally licensed being the most sensitive model; difference in regulatory opinions on assessment of similarity through acceptable endpoints and equivalent margins; and lack of acceptance of extrapolation across indications in different therapeutic areas by all regulatory agencies globally.

Similarly, Kirchoff CF et al (2017)[14] reported that regional and country specific biosimilar pathway legislation and guidances are at different stages of development and implementation as presented in figure 2.1. As a result, there is no global harmonization on certain aspects of biosimilar development, including as mentioned above; the selection of the reference product, nomenclature, and the design of analytical, non-clinical, or clinical comparative studies.

On the issue of interchangeability of biosimilars, there are major differences between Europe and the US when it comes to how they view interchangeability of biosimilars. Although EMA and FDA are aligned in most aspects of the concept of biosimilarity; the difference related to 'interchangeability' is attributed to a discrepancy in terminology and legal definition. In Europe, interchangeability is a scientific and medical term that refers to the medical practice of changing one medicine for another that is expected to achieve the same clinical outcome. The administrative practice of switching or substituting is a national decision. In the US, however, the legal definition of 'interchangeability' allows for substitution of the biosimilar for the reference product without the intervention of the prescriber[36].

2.6 Way forward

Kang et al (2018)35 noted that the main roles of regulatory authorities, for example, are to provide regulatory oversight of biosimilars throughout their product life-cycle and to ensure that only high-quality, safe and efficacious biosimilars are available on the market. This could be achieved by increasing the capacity of regulatory authorities. It was however noted that this is particularly challenging in resource –limited settings and therefore recommended that regulatory authorities in these settings consider establishing regulatory procedures that improve the efficiency of the approval process. For example, the established WHO global standards to ensure the quality, safety and efficacy of biotherapeutics, including biosimilars, at all stages of their life-cycle, could serve as a basis for mutual recognition of regulatory oversight and for regulatory convergence at the global level.

Harmonization of guidelines as the global biosimilar market continues to grow was proposed in a number of publications[2, 12, 14, 34].

Efforts are already being made to ensure regulatory harmonization of biosimilar requirements. A regulators forum37, the International Pharmaceutical Regulators Forum (IPRF) was created, as a safe harbor for discussion and promotion of harmonization among its members. Its membership is composed of regulatory authorities and agencies, regional harmonization initiatives and the WHO as indicated in table 2.4.

Table 2.4: Membership of the IPRF

Membership type	Members
Regulatory Authorities and Agencies	• Australia - Therapeutic Goods Administration (TGA) • Brazil - Brazilian Health Surveillance Agency (Anvisa) • Canada - Health Canada, Health Products and Food Branch • European Union – EMA and Directorate –General for Health and Consumers (SANTE) • Japan - Ministry of Health, Labour and Welfare, and Pharmaceuticals and Medical Devices Agency • Kazakhstan – National Center for Expertise • Republic of Korea – Ministry of Food and Drug Safety • Mexico – COFEPRIS (The Federation Commission for the Protection against Sanitary Risk) • Russia - Roszdravnadzor (Federal Service for Control over Healthcare and Social Development) • Singapore - Health Sciences Authority (HSA) • Switzerland - Swissmedic, Swiss Institute of Therapeutic Products • United States of America – U.S FDA
Regional Harmonization Initiatives	• APEC - (Asia-Pacific Economic Cooperation) • ASEAN - (The Association of Southeast Asian Nations) • EAC – (East African Community) • GCC (Cooperation Council for the Arab States of the Gulf) • PANDRH (Pan American Network for Drug Regulatory Harmonization) • SADC (Southern African Development Community)
WHO	

As mentioned above, one of the objectives of the IPRF is to identify the need for harmonization or regulatory convergence, as well as for regulatory cooperation, including work sharing, in specific areas. Several working groups are already in operation including the Biosimilars Working Group (BWG). The Biosimilars Working Group which is composed of international regulatory authorities has the following

objectives; for regulatory convergence of technical requirements for biosimilar products in facilitating the regulatory process; and to support international regulators develop safe and effective regulatory frameworks for biosimilar products.

The IPRF BWG has so far published a *Public Assessment Summary Information for Biosim*ilar (PASIB) dated 18 August 2016, intended to increase transparency and to facilitate the transition from a local assessment report to one prepared in the English language; and a *Reflection Paper on Extrapolation of Indications in Authorization of Biosimilar Products* dated 25 September 2017. The purpose of the reflection paper was to communicate the current thinking of various regulatory authorities of different regions with respect to the extrapolation of indications from the reference product to the biosimilar during the development of these products. It explored the issues associated with the use of extrapolation when authorizing biosimilar products for certain indications and proposed principles for the use of extrapolation in this context.

In an effort to create patient and healthcare professionals' awareness of biosimilars, on 13 September 2018, the European Medicines Agency (EMA) and the European Commission published new material, including an animated video for patients that explain key facts on biosimilars and how EMA works to ensure that they are as safe and effective as their reference biologicals. The video is available in eight European languages: Dutch, English, French, German, Italian, Polish, Portuguese and Spanish. In addition, EMA published translations of the biosimilar guide for healthcare professionals into Dutch, French, German, Italian, Polish, Portuguese and Spanish. The guide, which was first made available in English in 2017, provides healthcare professionals with comprehensive and easily understandable information on both the science and the regulation underpinning the use of biosimilars. These newly published materials complement the Questions & Answers on Biosimilars for patients, which were published in 23 EU languages in 201738.

Chapter Three: Work plan

3.1 Research question

Are the proposed biosimilars assessment guidelines of the NDA comparable to the EMA, WHO, USFDA and SAHPRA guidelines?

3.2 Aim

The aim of this study was to evaluate the current work done by NDA in development of biosimilars assessment (May 2018 draft) which started in November 2017, and make recommendations for inclusion based on WHO, EMA, US FDA and SAHPRA guidelines for biosimilars.

3.3 Objectives

The following were the research objectives:

1. To review the biosimilar assessment guidelines of the EMA, FDA, WHO and SAHPRA.
2. To compare the proposed NDA biosimilar assessment guidelines against those of EMA, FDA, WHO and SAHPRA
3. To review the proposed NDA guidelines generally to identify gaps or inconsistencies, if any
4. To make recommendations and inform NDA of areas for improvement within the guideline, and also based on best regulatory practices come across during literature review.

3.4 Rationale for chosen jurisdictions

3.4.1 EU

The biosimilars approval pathway was pioneered in the European Union (EU). The EU is by far the most advanced in the regulation of biosimilars, and has the best established framework for approval of biosimilars, being the first to create guidelines for these products. In the European Union (EU), the legal framework for approving biosimilars was established in 2003.

The EU biosimilars guidelines have formed the basis for development of biosimilars regulations in other highly regulated countries/regions e.g. Japan39 and other countries e.g. China40

3.4.2 WHO

The *Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)*, WHO 2009, are intended to provide globally acceptable principles for licensing biotherapeutic products that are claimed to be similar to biotherapeutic products of assured quality, safety, and efficacy that have been licensed based on a full licensing dossier. The Guidelines can be adopted as a whole, or partially, by NRAs worldwide or used as a basis for establishing national regulatory frameworks for licensure of these products.

Several countries including Canada, Brazil, South Africa, Japan, and Korea have used the principles for establishing biosimilarity outlined in the WHO guidance documents as a platform for authoring their national guidelines[14].

The WHO has a constitutional mandate to act as the directing and coordinating authority on international health work; and to develop, establish and promote international standards for food biological, pharmaceutical and similar products[41]. WHO through the Essential Medicines Program (EMP) works at country level, as well as regionally and globally, to support with norm setting and regulatory strengthening, and national level technical assistance and training. In the area of biosimilars, WHO is supporting countries in establishing the regulatory framework resources, and capacity to evaluate biosimilars, facilitate their uptake, and conduct post-marketing monitoring42. In addition, as mentioned in section 2.3.3, the WHO recently launched a pilot project to prequalify selected biologics and biosimilars, as a step forward to support national and global efforts to increase access to and the affordability of these products24.

3.4.3 U.S.A

The U.S FDA is the largest of the world's drug regulatory agencies, according to information on the ICH website[43]. Although the US lags behind the EU with respect to biosimilars regulation, it has developed extensive guidances on the regulatory requirements for the evaluation of biosimilars[14].

3.4.4 South Africa

South Africa was included to provide comparison with an African national medicines regulatory agency (NMRA). According to the ICH website, South Africa's SAHPRA is the first and currently the only African NMRA to obtain ICH observer status which is a step towards achieving membership status[44]. It was stated that becoming a member of the ICH Association sends a clear message that the regulatory authority and the regulated industry are committed to align with the highest global standards for the quality, efficacy and safety of medicinal products. Membership in ICH brings with it integrity and recognition worldwide45.

Since information on biosimilars regulation in Africa with respect to status in the different NMRAs, was not readily available, the fact that South Africa has ICH observer status and that biosimilar guidelines are readily available online, contributed to its selection.

Chapter Four: Methodology

4.1 Introduction

The two main types of research design methods are qualitative and quantitative methods. The simple distinction between the two methods is that qualitative data analysis deals with the analysis of subjective and non-numerical data while quantitative data analysis focuses on analyzing data through a numerical or statistical means46. Quantitative methods are used to examine the relationship between variables with the primary goal being to analyze and represent that relationship mathematically through statistical analysis. This is the type of research approach most commonly used in scientific research problems [46].

Qualitative methods are chosen when the goal of the research problem is to examine, understand and describe a phenomenon. These methods are a common choice in social science research problems and are often used to study ideas, beliefs, human behaviors and other research questions that do not involve studying the relationship between variables[46].

Therefore, it is often said that quantitative research seeks to *explain* and qualitative research seeks to understand[46].

The purpose of the research was to assess the current work done in the development of biosimilar guidelines by NDA, Uganda, and make recommendations for inclusion mainly based on the EU, South African, U.S.A and WHO biosimilar guidelines. It was exploratory in nature and sought to examine and understand the works done by NDA this far. The data is non-numerical and the research is qualitative in nature.

4.1.1 Qualitative research methods

There are five main types of qualitative research designs commonly used: narrative, phenomenology, grounded theory, ethnography and case study[46].

Table 4.1: Summary of qualitative research approaches and their characteristics[46]

	Narrative	Phenomenology	Grounded Theory	Ethnography	Case study
Focus	Explores the life of an individual; tells the story	Attempts to understand or explain life experiences or a phenomena	Investigates process, action or interaction with goal of developing a theory "grounded in observations	Describes and interpretes ethnic, cultural, or social group	Examines episodic event in a definable framework; develops in depth analysis single or multiple cases; generally explaining "how"
Data collection	Interviews and documents	Prmarily through interviews, sometimes observation	Interviews with 20-30 individuals to gather enough data	Interviews, observations, and immersion into the cultural as an active participant	Documents of the case, archives, interviews, observations, physical artifacts
Data analysis	Stories , review of historical content, development of themes	Study and describe experiences, examine meaning and context, look for themes, classify	Open, axial, and selective coding used to categorize the data and describe the implications of the categories	Describe and interpret findings by analyzing data and developing themes	Develop a detailed analysis; identify themes; make assertions
Written Report Form	Detailed picture of person's life; often a chronology or biography	Report of "essence" of the experience, description of the context of the experience or phenomena	Results in a theory, theoretical model, or figure that represents the phenomena	Description of the cultural behaviour of a group	In-depth study of a case that describes the case, its themes, and possible lessons learned

The research followed the case study approach based on a comprehensive literature review. The narrative, phenomenology, grounded theory and ethnography approaches focus on telling a story; understand a phenomena; investigation of an action with the goal of developing a theory; and describe and interpret ethnic cultural or social groups respectively, none of which was the focus of the research. The purpose of the research was to evaluate and assess critically the NDA draft biosimilar guideline which was in line with the case study approach.

Case studies are analyses of persons, events, decisions, periods, projects, policies, institutions, or other systems that are studied holistically by one or more methods. The case study can be done in social sciences and life sciences. Case studies may be descriptive or explanatory. Like surveys, case study research approaches can be treated as a qualitative or quantitative[47].

A comprehensive literature-based review is described as "an iterative, thematic approach to research where qualitative analysis is used to classify information contained in literature and come to a conclusion on the basis of qualitative description"[4849]. Qualitative analysis has value in comparing literature, analyzing and proposing alternative strategies48. Criticism of the literature-based review method is that it is not methodological, has no clear-cut design, lacks transparency of the method and cannot be duplicated50. Additionally, the possibility of potential bias or selection bias is high[51]. Low retrievability of data is also raised as a disadvantage to the use of this type of research. The significant difference from other methodologies is that it does not directly deal with the object under study but indirectly accesses information from a variety of literature52.

The table below provides an overview of the most common types of qualitative data collection approaches. It includes description, advantages, disadvantages and list of appropriate qualitative approaches.

Table 4.2: Overview of the most common types of qualitative data collection46

Method and Description	Advantages	Disadvantages	Appropriate for these Approaches
Structured Interviews: One-on-one interview using predetermined questions	Easy to administer; quicker than other interviews	Does not allow for follow up or variation; may lack depth	Phenomenology; Grounded Theory; Ethnography; Case Study
Unstructured Interviews:	More in-depth; allows	More time-consuming; less	Narrative; Phenomenology;

No standard set of questions, often used to explore an idea; can use open-ended questions	interviewer to follow up; less rigid; more open responses	consistency in data collected	Ethnography; Case Study
Focus Groups: Group interview that uses group interactions to help formulate thoughts/ideas	More time-effective; gather information from multiple people at once; provides social context	Group dynamics can sometimes interfere with accuracy of the data; number of questions must be limited	Grounded; Theory; Ethnography; Phenomenology
Direct Observation: Research gathers first hand data on programs, processes or behaviors through direct observation and note-taking	Can gain a holistic perspective by seeing full context; researcher can look for unexpected outcomes; occurs in the natural setting	Time-consuming; may effect behaviour of participants; perceptions of observer influence the data; may be intrusive	Phenomenology; Ethnography; Case Study
Participant Observation: Researcher participates in activities rather than just observing; active participation/observation	Active participation provides more complete understanding and context; may be more natural/less intrusive	May become too close to the topic or to the people involved in the study; may lose objectivity	Ethnography; Case Study
Written Documents: Researcher uses existing documents such as letters, memos, diaries, emails and so forth to study topic	May provide factual information otherwise not attainable if writers are deceased: inexpensive	May be subjective data from point of view of the writer; may be difficult to verify validity; may find conflicting information	Narrative; Case Study
Artifacts: Researcher study items made/used by different societies and cultures that provide evidence of the past	Provides insight into how people lived, what they believed and valued, their knowledge and options	May be difficult to interpret meaning and use; needs to be analyzed in appropriate context; often used in conjunction with other methods	Narrative; Case Study

4.1.2 Qualitative data analysis

There are a variety of approaches to this process of analysis and interpretation. Some of the most commonly used approaches include46, [53]:

- Thematic analysis – details below in 4.1.2.1

- Content Analysis - used to analyze and interpret verbal data, or behavioral data. Content can be analyzed for descriptively or interpretatively.
- Narrative Analysis - used to analyze text that may come from variety of sources including transcripts from interviews, diaries, field notes, surveys and other written forms. Narrative analysis often involves reformulating stories presented by people in different context and based on their different experiences.
- Discourse Analysis - a method of analyzing naturally occurring spoken interactions and written text and is concerned with the social context in which the communication occurred. It focuses on how language is used in everyday life and looks at how people express themselves.
- Grounded Theory - also called analytic induction. This is a method that attempts to develop causal explanations of a phenomenon from one or more cases being studied. Explanations are altered as additional cases are studied until the researcher arrives at a statement that fits all cases.
- Conversation Analysis - examines the use of language by people as a type of action or skilled accomplishment. A key concept in this analysis is the principle of people taking turns in conversation. Meanings are usually shaped in the context of the exchange itself.

Those are some of the most common methods. However, there are about fifteen methods including typology, taxonomy, analytic induction, logic analysis, quasi-statistics, event analysis, metaphorical analysis, domain analysis, hermeneutical analysis and semiotics54.

4.1.2.1 Thematic analysis

Thematic analysis is the process of identifying patterns or themes within qualitative data. Braun & Clarke (2006) suggest that it is the first qualitative method that should be learned as '….it provides core skills that will be useful for conducting many other kinds of analysis' (p.78). A further advantage, particularly from the perspective of learning and teaching, is that it is a method rather than a methodology (Braun & Clarke 2006; Clarke & Braun, 2013). This means that, unlike many qualitative methodologies, it is not tied to a particular epistemological or theoretical perspective. This makes it a very flexible method, a considerable advantage given the diversity of work in learning and teaching53. The goal of a thematic analysis is to identify themes, i.e. patterns in the data that are important or

interesting and use these themes to address the research or say something about an issue. Braun & Clarke (2006) distinguish between two levels of themes: semantic and latent. Semantic themes '…within the explicit or surface meanings of the data and the analyst is not looking for anything beyond what a participant has said or what has been written.' (p.84). The analysis in this worked example identifies themes at the semantic level and is representative of much learning and teaching work. We hope you can see that analysis moves beyond describing what is said to focus on interpreting and explaining it. In contrast, the latent level looks beyond what has been said and '…starts to identify or examine the underlying ideas, assumptions, and conceptualizations – and ideologies - that are theorized as shaping or informing the semantic content of the data' (p.84) [53].

4.2 Research Approach

This study employed the principles of explorative comprehensive literature-based review using a thematic qualitative approach. The method of data collection was documentation, collected and selected using document review and analysis. The methodology chosen was in keeping with the aims and objectives of the study to critically evaluate the proposed NDA biosimilar assessment guidelines with comparison of the proposed guidelines with those from chosen jurisdictions; and make recommendations for identified gaps, and also provide recommendations for best regulatory practices come across during the literature search. The chosen jurisdictions were the EU (EMA), South Africa (SAHPRA), USA (U.S.FDA) and WHO.

The distinction between qualitative and quantitative research is a methodological issue. A comprehensive literature-based review is described as "an iterative, thematic approach to research where qualitative analysis is used to classify information contained in literature and come to a conclusion on the basis of qualitative description"48. Qualitative analysis has value in comparing literature, analyzing and proposing alternative strategies48. This was therefore the method of choice for the research. A review of the various qualitative research approaches to data analysis revealed that the thematic analysis method was most suited for the research project. For the project, themes obtained from the proposed NDA biosimilar guidelines were identified. Data was then organized into major themes and categories. Critical evaluation and assessment of the information under the various themes was performed using document analysis. Document analysis is defined as a —systematic procedure for reviewing or evaluating documents[51]. It requires that data be examined and interpreted in order to elicit

meaning, gain understanding and develop empirical knowledge, by finding, selecting and appraising data contained in documents[55].

Document analysis also included comparison with guidelines from the chosen jurisdictions. A discussion of the results obtained and information gathered then followed. Experiences of practices in the various jurisdictions were evaluated some of which formed recommendations for inclusion in the proposed NDA guidelines.

4.3Data collection

The method of data collection was documentation, collected and selected using document review and analysis. Documentation used for the research was obtained by internet search, using the google search engine. Key words used for the search included: *biosimilars, regulation of biosimilars, demonstration of biosimilarity, challenges in biosimilars regulation, future of biosimilars, opportunity for biosimilars, biosimilars and interchangeability, extrapolation of indications with respect to biosimilars* and so on. The websites for the regulatory agencies in the chosen jurisdictions were also visited and available information on biosimilars reviewed. In order to keep up to date with recent developments for biosimilars, subscription was made to the Generics and Biosimilars Initiative (GaBi) and Biosimilar Development online journals. FDA's Overview of Biosimilars online course19, was also taken with a certificate of completion awarded.

To evaluate the NDA's draft biosimilar assessment guidelines, data was organized into themes, and parameters for review and/or comparison were identified as follows. These were largely based on the structure in the proposed NDA biosimilar guidelines.

- Structure/guideline organization
- Table of contents -
- Terminology used
- Definition (for biosimilars) as stated in guidelines
- Introduction
    - The concept of Similar Biotherapeutic products

- General information
  - Considerations for the choice of Reference Biotherapeutic Product (RBP)
- Other requirements
  - Manufacturer's declaration
- Submission requirements
  - Module 1: Administrative and Product Information
  - Module 2: Overview and summaries
  - Module 3: Quality
    - Qualitative and Quantitative Particulars
    - Manufacturing Process
    - Analytical Comparability
    - Analytical Procedure/technique/product Characterization
  - Module 4: Non Clinical Study
    (Special consideration, pharmacodynamics, toxicology)
  - Module 5: Clinical study
    (Pharmacokinetic (PK) Studies, pharmacodynamic (PD) Studies, clinical efficacy trials, Clinical safety and effectiveness, clinical Immunogenicity and pharmacovigilance)
- Other guideline related documents: Summary Information for Similar Biotherapeutic Product (SIB) - Appendix 2
- Other principles
  - Policy on interchangeability
  - Possibility of extrapolation of efficacy and safety from one therapeutic indication to another

In keeping with the research objectives, the above criteria were used to critically review NDA's proposed guideline. The various parameters especially the technical requirements (Module 3: Quality considerations, module 4: non-clinical requirements, and module 5: clinical requirements), were compared with those in biosimilar guidelines from the chosen jurisdictions and also with related information on the official websites of these jurisdictions. In addition, a review of the entire guideline

was performed to identify inconsistencies. Review was not performed for certain sections. These were mentioned and justification for exclusion provided.

The following guidelines obtained from the respective country/agency websites were reviewed in addition to the information on the websites. The scope of the proposed NDA guidelines is stated as "…These guidelines apply to well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins. Vaccines and plasma derived products and their recombinant analogues are excluded from the scope of these guidelines…." Therefore, only the biosimilar guidelines from the chosen jurisdictions that fall within this scope were selected.

Table 4.3: Biosimilar Guidelines reviewed.

Jurisdiction	Guideline(s) name	Current version date	Reference
EU	*Overarching biosimilar guidelines*		
	Guideline on similar biological medicinal products	23 October 2014	https://www.ema.europa.eu/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf
	Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues	18 December 2014	https://www.ema.europa.eu/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf
	Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)	22 May 2014	https://www.ema.europa.eu/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-0.pdf
	Biosimilars in the EU – Information guide for healthcare professionals**	May 2017	https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf
SA	Biosimilar Medicines Quality, Non-clinical and Clinical Requirements*	August 2014	https://www.sahpra.org.za/documents/d259816c2.30_Biosimilars_Aug14_v3.pdf

Uganda	Guidelines for Registration of Similar Biotherapeutic Products	30 May 2018	Obtained from the Product Assessment and Registration directorate (NDA) – *Refer to annexex 1 and 2.*
USA	Scientific Considerations in Demonstrating Biosimilarity to a Reference Product	April 2015	https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf
	Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product	April 2015	https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf
	Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product	December 2016	https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf
WHO	Guidelines on evaluation of Similar Biotherapeutic Products (SBPs), Annex2, Technical Report Series No. 977, 2009	2009	http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf?ua=1
	WHO Guidelines on submission of documentation for the pilot procedure for prequalification of similar biotherapeutic products for rituximab and trastuzamab (full assessment)	June 2018	http://www.who.int/medicines/regulation/prequalification/02_GLs_Submission_Pilot_FullPathway_2018.pdf?ua=1

*Annexure 1: *Product Class Specific for Monoclonal Antibodies* was not considered for this research.

**Included for the glossary of terms contained therein, that is applicable to biosimilars. The EU overarching guidelines do not contain glossary of terms.

4.4 Ethical considerations

An official request to use NDA's draft biosimilar assessment guideline for research purposes including request for a copy of the same, was sent by email to the NDA, Director of Product Assessment and Registration on 24 October 2018. Permission was granted on 26 October 2018, and a copy of the draft guidelines was provided. A copy of the permission letter and email correspondences is attached in

appendix II. A copy of the proposed NDA biosimilar guideline is attached in appendix III. In the letter, a commitment was made to share research findings with NDA upon completion. The findings and recommendations were shared with NDA on 01 March 2019.

Chapter Five: Results and Discussion

5.1 Overall Structure/organization of guidelines

This section was not subjected to comparison with other biosimilar guidelines from the chosen jurisdiction because it has no impact on the quality, safety and efficacy of biosimilars. Organization of guidelines is a country specific decision. Therefore, the proposed structure of the NDA guideline was reviewed. The guideline follows a CTD format, detailed in the proposed NDA guideline for registration of biotherapeutics which is also currently under preparation. The proposed biosimilar guideline makes reference to the proposed Biotherapeutics guideline for guidance on structure. The guidance is presented in a modular approach as follows,

- Module 1: Administrative and Product Information
- Module 2: Overview and summaries
- Module 3: Quality
- Module 4: Non Clinical study
- Module 5: Clinical study

According to information on the ICH website56, the agreement to assemble all the Quality, Safety and efficacy information in CTD format has revolutionized the regulatory review process, led to harmonized electronic submission that, in turn, enabled implementation of good review practices. For pharmaceutical manufacturers, it has eliminated the need to reformat the information for submission to the different regulatory agencies. It was initially designed to provide a common submission format between Europe, USA and Japan but it has now been accepted and implemented worldwide for regulatory submissions. According to the WHO guideline for the biosimilars pilot project57, many countries that import WHO prequalified medicinal products require the submission of a product dossier

in CTD format for registration of the products. The CTD format is therefore an acceptable form of submission of marketing authorization applications.

5.2 Table of contents and glossary of Terms

The table of contents was checked for accuracy and for inconsistencies. The proposed hyperlinks were working as intended and with the exception of a minor topographical error noted for part 2.2, no gaps were identified. In part 2.2, it was stated as *Consideration For The Choice of Rbp* instead of *Consideration for the choice of RBP* as stated in the body of the guidelines.

The proposed glossary of terms was reviewed and checked for consistency with the purpose of identifying gaps. In addition, the terms and definitions were compared with those in guidelines from the chosen jurisdictions.

For the consistency check, the proposed glossary terms were checked for inclusion in the body of the guideline. With the exception of the following, all terms defined were included in the body of the guideline. The following terms were defined in the glossary of terms but were not included in the guideline body: *Genetic engineering* and *in-process control*. It is recommended that the reference documents that were used to prepare the guidelines are revisited to consider either inclusion in the guidelines or exclusion, as considered appropriate.

The terms and definitions were compared with those in guidelines from chosen jurisdictions to check whether they are comparable. Only the terms with concerns and recommendations for inclusion are discussed.

5.2.1 Bioequivalence

The proposed NDA definition is "*Two proprietary preparations of a drug, when administered in the same dose and by the same route, will have the same bioavailability, duration of action and efficacy.*"
It was observed that bioequivalence was not defined in any of the guidelines reviewed from the chosen jurisdictions. However according to WHO's Guidance for organizations performing in vivo

bioequivalence studies (Annex 9, Technical report series no. 996, 2016); "*Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of rate (Cmax and tmax) and extent of absorption (area under the curve), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same."*[58] In the document Biosimilars in the EU-Information guide for healthcare professionals[59] bioequivalence is defined as "*when two medicines release the same rate and to the same extent under similar conditions*."

The proposed NDA definition is in line with the above definitions. However the term 'bioavailability' was not defined. Therefore, it is recommended that the definition be revised to include an explanation of the term. The WHO definition provides an extensive and complete definition which may be adopted.

5.2.2 Biotherapeutics

The proposed NDA definition is "*therapeutic biological products, some of which are produced by recombinant DNA technology."* The definition makes reference to the terms *biological products* and *recombinant DNA technology*, which are also mentioned in the guideline but have not been defined.

Of the guidelines reviewed, from the chosen jurisdictions, only the South African and U.S.FDA guides had a definition for biological products, as in Table 5.1.

Table 5.1: Definition for biological products in South African (SAPHRA) and U.S.A (U.S.FDA) biosimilar guidelines

South Africa	Biological Medicine: All medicines that contain a living organism, or are derived from a living organism or biological processes are considered Biological Medicines. They include, but are not limited to the following: i. Plasma-derived and animal products, e.g. Clotting factors, Immunosera, Antivenoms ii. Vaccines iii. Biotechnology-derived medicines (rDNA products) e.g. rHu-antihaemophilic factors, hormones, cytokines, enzymes, monoclonal antibodies, erythropoietins, nucleic acids; iv. Products developed for Human Gene therapy.

U.S. A	Biological product: Virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Both the above definitions are comprehensive. NDA may consider combining both definitions to come up with a comprehensive definition. The proposed definition for biological product based on the South African and U.S.A guidelines is "All products that contain a living organism, or are derived from a living organism or biological processes, applicable to the prevention, treatment, or cure of a disease or condition of human beings are considered biological products. These include viruses, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound)."

For Recombinant DNA technology, the term was only defined in the EU information guide to healthcare professionals as "Technology that involves combining sequences of DNA that do not occur naturally, for example inserting a gene for producing a therapeutic protein." This definition may be adopted by NDA.

5.2.3 Comparability Exercise

Comparability exercise is defined as "activities including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable (head to head comparison)," in the proposed NDA guideline. Head-to-head comparison is defined further on in the guideline. Of the guidelines reviewed, only the WHO and EU information guide to the health care providers have definitions for comparability exercise.

Table 5.2: Definition for comparability exercise in the EU and WHO biosimilar guidelines

EU	Head-to-head comparison of a biosimilar with its reference medicine to rule out any significant differences between them in terms of structure and function. This scientific principle is routinely used when a change is introduced to the manufacturing process of medicines made by biotechnology, to ensure that the change does not alter safety and efficacy.
WHO	Head-to-head comparison of a biotherapeutic product with a licensed originator product with the goal of establishing similarity in quality, safety and efficacy. Products should be compared in the same study using the same procedures.

Comparison of the above definitions with the proposed NDA definition showed that the NDA definition could be improved and made more specific.

The EU and WHO definitions are both comprehensive and take into account all aspects to be considered during a comparability exercise, that is to say; quality, safety and efficacy. It is therefore proposed that NDA adopts either of these definitions.

5.2.4 ICH

ICH is defined as follows in the proposed NDA guideline;

"Means International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. For more information, see http://www.ich.org/."

According to the ICH website[44], the membership of ICH has since grown and the list of observers increased. It is therefore proposed that NDA updates its definition in line with current information on the website. Alternatively, the definition may be deleted from the glossary of terms and instead included

in the list of abbreviations, with a link to the website. This will ensure that the ICH related information in the guideline is up to date.

5.3 Terminology and Definition

Table 5.3: Definition for Biosimilars/Similar Biotherapeutic Products (SBPs) in the proposed Uganda guideline and selected jurisdictions

Country	Terminology and Definition
Uganda	Similar Biotherapeutic Products (SBP)/Biosimilar The terms *Similar biotherapeutic products* and *Biosimilars* are used interchangeably throughout the guideline. A new biotherapeutic product claimed to be similar" to an already approved reference biotherapeutic product, which is marketed by an independent applicant, subject to all applicable data protection periods and/or intellectual property rights in the innovator product. The requirements for the registration of similar biotherapeutic product are based on the demonstration of similarity (i.e. no clinically meaningful difference between the similar biotherapeutic product and the reference biotherapeutic product) in terms of quality, safety and efficacy to an already registered, reference biological product.
EU	Similar biological medicinal products/Biosimilars (The terms *Similar biological medicinal products* and *Biosimilars* are used interchangeably throughout the three (3) overarching guidelines.) A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product) in EEA.
South Africa	Biosimilars A biosimilar is a biological medicine that is similar, but not necessarily identical, in terms of quality, safety and efficacy to an already registered reference biological medicine. It is synonymous with *follow-on biologics* and *similar biotherapeutic products*.
U.S.A	Biosimilar A biosimilar is a biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the biological product and the reference product

	in terms of safety, purity and potency of the product.
WHO	Similar biotherapeutic product (SBP) A biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

The different terminologies used for biosimilars in the chosen jurisdictions are stated in the table above. The terminology in the proposed NDA biosimilar guideline of *Similar Biotherapeutic Products* is the same as that used in the WHO biosimilar guidelines.

The difference in terminologies for biosimilars is however a cause for concern. The WHO guideline states that a variety of terms have been coined to describe these products, such as *biosimilar products*, *follow-on protein products* and *subsequent-entry biologics*. According to the articles *Terminology for biosimilars – a confusing minefield60,* and *Comparison of Global Regulatory Approvals for Biosimilar products*[61], the inconsistency in nomenclature used for biosimilars has led to confusion in referring to some products. According to the publications, this confusion is not just a potential concern for patient safety and efficacy, but can also lead to misconceptions which arise from misleading published reports on apparent problems with biosimilars.

Several examples of misleading published reports have occurred, however, the most cited case is that of pure red cell aplasia in later stages of adrenal disease patient associated with stimulation of antibodies to administered erythropoietin (EPO) was seen in India. The patient had taken the EPO product Wepox (Wockhardt Limited, India) that was referred to as a 'follow on' product (biosimilar).However, there was no evidence that this product had been approved using the comparability approach required in the EU for biosimilarity and described in the WHO and other guidelines. This was in fact considered unlikely as the Indian regulatory process at the time did not include biosimilars (or follow-on products). The product Wepox is therefore not a biosimilar and should not have been described as such[60,61]. It was a clear misuse of terminology. It is therefore important that the terminologies are harmonized to avoid confusion.

The definition for biosimilars across the five (5) jurisdictions is the same in principle with the exception of differences in wording. The major difference lays in the requirement for the reference biological products which will be discussed in detail under section 5.5.

5.4 Introduction

5.4.1 The concept of Similar Biotherapeutic products

Table 5.4: Concept for establishing biosimilarity in the proposed Uganda guidelines and selected jurisdictions

Uganda	Based on the comparability approach and when supported by state-of-the-art analytical systems, the comparability exercise at the quality level may allow 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 aim of the biosimilar approach is to demonstrate close similarity of the 'similar biotherapeutic product' in terms of quality, safety and efficacy to one chosen reference medicinal product, subsequently referring to the respective dossier.
EU	**Stepwise approach recommended throughout the development programme:** Starting with a comprehensive physicochemical and biological characterization (analytical studies and *in vitro* pharmaco-toxicological studies) ↓* Extent and nature of the non-clinical *in vivo* studies and clinical studies depend on the level of evidence obtained in the previous step(s). In specific circumstances, a confirmatory clinical trial may not be necessary. This requires that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and the reference product. In addition, it requires that the impurity profile and the nature of excipients of the biosimilar itself do not give rise to concern. The ultimate goal of the biosimilar comparability exercise is to exclude any relevant differences between the biosimilar and the reference medicinal product. If the biosimilar comparability exercise indicates that there are relevant differences between the intended biosimilar and the reference medicinal product making it unlikely that biosimilarity will eventually be established, **a stand-alone development to support a full Marketing Authorisation Application should be**

	considered instead.
South Africa	Applicant should carry out a comprehensive physicochemical and biological (*in vitro*) characterization of the biosimilar API substance; each of these analyses must be conducted in a head-to-head comparison with the reference API substance. A lack of detectable, relevant differences between the biosimilar and the reference medicine is the basis for reducing non-clinical and clinical requirements for registration.
U.S.A	Stepwise approach is recommended. At each step, the sponsor should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product and identify next steps to try to address that uncertainty. Extensive structural and functional characterization of the proposed product and the reference product* ↓ Consider the role of animal data in assessing toxicity and, in some cases, in providing additional support for demonstrating biosimilarity and in contributing to the immunogenicity assessment ↓ Conduct comparative human PK and PD studies and compare the clinical immunogenicity of the two products in an appropriate study population ↓ Comparative clinical study(ies) data If there is residual uncertainty about biosimilarity after conducting structural analyses, functional assays, animal testing, human PK and PD studies, and the clinical immunogenicity assessment, the sponsor should then consider what additional clinical data may be needed to adequately address that uncertainty * The more comprehensive and robust the comparative structural and functional characterization. The extent to which these studies are able to identify (qualitatively or quantitatively) differences in relevant product attributes between the proposed product and the reference product (including the drug substance, excipients, and impurities)—the more useful such characterization will be in determining what additional studies may be needed. For example, rigorous structural and functional comparisons that show minimal or no difference between the proposed product and the reference product will strengthen the scientific justification for a selective and targeted approach to animal and/or clinical testing to support a demonstration of biosimilarity.
WHO	Stepwise approach recommended: Characterization and evaluation of quality attributes of the product ↓

	Nonclinical studies ↓ Clinical studies Comprehensive characterization and comparison showing similarity at the quality level are the basis for possible data reduction in the nonclinical and clinical development. Any underlying differences should be fully explained and justified and may lead to additional data.

*The symbol "↓" shows the stepwise approach in establishing biosimilarity. Requirements at a stage must be fulfilled before proceeding to the next.

As stated in the table above, all guidelines in the five (5) jurisdictions recommend a stepwise approach for establishing biosimilarity. They require a comprehensive comparison of the quality attributes of the biosimilar and reference products. Fulfilment of this requirement determines the need and amount of additional studies required i.e. non-clinical and clinical studies. A risk-based approach is used to evaluate all data and information in support of the biosimilarity of the proposed product. In all jurisdictions, applicants may be able to demonstrate biosimilarity even though there are formulation or minor structural differences, provided sufficient data and information demonstrating that the differences are not clinically meaningful is provided. However, the EU and U.S.A guidelines provide much more detailed information on the biosimilarity approach in comparison to the other jurisdictions. The types of studies at each step are specified. In addition, the clinically meaningful differences are defined. Statements from either the EU or U.S.A guidelines or a combination of the two (2) may be adopted in the proposed Uganda guidelines. This will provide further clarity to the applicants during product development and information to be submitted in the application.

5.5 General information

Table 5.5: Considerations for choice of reference products(s) in the proposed Uganda guidelines and selected jurisdictions

Jurisdiction/Country	RBP should have marketing authorization in Jurisdiction or country	Consideration for RBP(s) with no marketing authorization in jurisdiction or country	Use of single RBP throughout the comparability programme	Use of more than one RBPs during the comparability programme
EU	√ RBP must be authorized in EEA	√ Possibility for applicant to compare the biosimilar in certain clinical studies and *in vivo* non-clinical studies (where needed) with a non-EEA authorized comparator authorized under similar scientific and regulatory standards as EMA (e.g. ICH countries)*.	√	√ Combined use of EEA authorized reference product and non-EEA authorized comparator is acceptable for the development of the Quality Target Product Profile of biosimilar product
South Africa	√ RBP must be registered in South Africa**	x	√	x
WHO	N/A The RBP should have been marketed for a suitable duration and have a volume of marketed use such that the demonstration of similarity to it brings into relevance a substantial body of acceptable data regarding the safety and efficacy. The RBP should be licensed and widely marketed in		N/A The same RBP should be used throughout the development of the SBP (i.e. throughout the comparative quality, nonclinical, and clinical studies)	

	another jurisdiction that has a well-established regulatory framework and principles, as well as considerable experience of evaluation of biotherapeutic products and post-marketing surveillance activities. The acceptance of an RBP for evaluation of an SBP in a particular country does not imply that the NRA of that country has approved the RBP for use.			
Uganda	WHO recommendation fully adopted		WHO recommendation fully adopted	
U.S.A.	√ RBP should have been previously licensed by U.S FDA	√ Possibility for applicant to use data derived from non-clinical or clinical comparing proposed biosimilar product with a non-U.S.-licensed comparator product*	√	X

√ - Yes

X – No

N/A – Not applicable. Recommendations included.

*Applicant is required to provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the U.S.-licensed RBP or EEA authorized RBP.

**RBP must be sourced from a country that MCC (SAHPRA) aligns itself with.

The EU, South Africa and U.S.A all require the RBP to have been licensed by their respective agencies. Both the EU and U.S.A provide for RBPs not licensed by their agencies, however, the alternative RBP should have been authorized under similar scientific and regulatory standards as EMA e.g. ICH countries or in the case of U.S.A, the applicant is required to provide adequate data or information to scientifically justify the relevance of the comparative data of the alternative RBP to an assessment of biosimilarity and establish an acceptable bridge to the U.S.-licensed RBP or EEA authorized RBP.

Uganda adopted WHO's recommendation for the RBP. However, there is need for the requirements to be updated to suite Uganda. The proposed requirement is "The RBP should be registered in Uganda and/or by a stringent regulatory agency (SRA); and should have been marketed for a suitable duration

and have a volume of marketed use such that the demonstration of similarity to it brings into relevance a substantial body of acceptable data regarding the safety and efficacy."

The definition of an SRA has evolved over the years; however, the following WHO interim definition may be used62:

- a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; or
- an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or
- a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015).

All jurisdictions including Uganda require use of single RBP throughout the comparability programme. The EU however has provision for combined use of EEA authorized reference product and non-EEA authorized comparator for only the development of the Quality Target Product Profile of biosimilar product.

Sourcing of the RBP is mentioned in the South African guideline. It is stated that the RBP should be sourced from a country that MCC (SAHPRA) aligns itself with. It is also expected that the RBP should be sourced from the EU or USA respectively in the case of EMA and U.S.FDA, or from countries that the two align themselves with as stated in the table. Sourcing of the RBP is however not mentioned in the proposed guidelines for Uganda. Provision for sourcing of RBP should be made in the guideline. The following information from the WHO website in reference to a bioequivalence study comparator product may provide useful guidance[63]: "To prove the origin of the comparator product, the applicant must include the following documents in the product dossier submitted for evaluation:

- copy of the RBP labelling which should include: the name of the product; name and address of the manufacturer; batch number; and expiry date (clearly visible on the labelling)

- copy of the invoice from the distributor or company from which the RBP was purchased; the address of the distributor must be clearly visible on the invoice
- documentation verifying the method of shipment and storage conditions of the RBP from the time of purchase to the time of study initiation
- a statement — by the company executive responsible for the application for registration certifying the authenticity of the above documents and that the RBP was purchased from the specified national market."

5.6 Other requirements

This section was considered administrative and was not included in the research. However, the statement below under section 2.4.1 of the guideline was reviewed with a recommendation based on experiences from stringent regulators.

5.6.1 Manufacturer's declaration

"The applicants intending to develop SBPs should meet with regulators in their country of origin to present their product development plans and establish a schedule of milestones that will serve as standards for future discussions with the respective regulators."

Pre-submission meetings are very beneficial especially for complex medicinal products such as biosimilars. According to the Australian Government Department of Health Theraputic Goods Administration (TGA) website, the meetings help both the applicant and the agency to obtain a common understanding of the medicinal product, the supporting documentation needed to evaluate the application, any issues that need to be resolved before submitting applications; plan for submission and management of both timeframes and resources.

Stringent regulators like; US FDA64, EMA[65] and TGA[66] have detailed guidance documents for pre-submission meetings posted on their respective websites. The WHO Prequalification of medicines websites also has information and guidance notes on pre-submission meetings on its website.
It is therefore recommended that NDA drafts a guidance document(s) for pre-submission meetings and preferably publish on the NDA website.

5.7 Submission requirements

The proposed format for submission of biosimilar applications to NDA is the ICH CTD format, as in 5.1.

5.7.1 Module 1: Administrative and Product Information

Module I of the CTD is administrative in nature and country or region specific. This will therefore be excluded from the comparison and research.

5.7.2 Module 2: Overview and summaries

Module 2 contains summaries of the quality (chemical, pharmaceutical, and biological) nonclinical and clinical information presented in modules 3, 4 and 5 of the CTD marketing authorization application. This will be excluded from the comparison and research.

5.7.3 Module 3: Quality

The quality aspects specific to biosimilars were compared. It is expected that much more information required for biologicals will be submitted as stipulated in the respective country or region guidelines for registration on biotherapeutic products.

Table 5.5: Qualitative and Quantitative Particulars

	Uganda	EU	South Africa	U.S.A	WHO
Requirement: List of all components of the biosimilar and diluents if applicable	√	√	√	√	√
Quantity per dose					
Name of active ingredient					
Special excipient characteristics e.g. water (purified, demineralized)					

Table 5.6: Manufacturing Process

	Uganda	EU	South Africa	U.S.A	WHO
The quality target product profile (QTPP) forms basis for development of biosimilar product and manufacturing process. Biosimilar is manufactured and controlled according to its own development taking into account state-of –the- art-information on manufacturing processes and consequences on product characteristics	√	√	√	√	√
Demonstration of similarity:					
Differences between the chosen expression system of the proposed SBP and that of the RBP should be carefully considered and appropriately documented	√	√	√	√	√
Characterization of the expression construct, including its genetic stability, should be demonstrated in accordance with principles recommended in ICH Q5					
Characterization tests, process controls, and specifications that will emerge from information gained during process development must be specific for the proposed SBP and the manufacturing process.					
Full Drug Master File (DMF), manufacturing process validation protocol and report should be submitted	√	√	√	√	√
Product employing clearly					

different approaches to manufacture from the reference product will not be eligible for registration as a SBP.					

Table 5.7: Analytical Comparability and Analytical Procedure/technique/product Characterization

Summary of analytical considerations	Extensive state-of-the-art characterization studies applied to the biosimilar and reference medicinal products in parallel
	Selected methods for comparability exercise should have ability to detect relevant variants with high sensitivity
	Characterizations to include determination of physicochemical properties, biological activity, immunochemical properties, purity, impurities, contaminants, and quantity. Product-related impurities, product-related substances, and process-related impurities should be identified, characterized as appropriate, quantified and compared to those of the RBP to the extent feasible and relevant, as part of an assessment of the potential impact on the safety, and potency of the product.
Uganda	√
EU	√
South Africa	√
U.S.A	√
WHO	√

The quality related principles required for establishing biosimilarity are the same across the selected jurisdictions including Uganda, although the EU and U.S.A guidelines provide in-depth information and explanations of the various principles. The proposed Uganda guideline makes reference to the EU and ICH guidelines for more detailed information.

Quality principles include characterization of the reference product, analytical characterization of the biosimilar and, structural and functional comparison.[68] The reference product is characterized to identify the product's critical quality attributes (CQAs), characteristics that affect identity, purity, biological activity, and stability of a drug.

For analytical characterization of the biosimilar, the biosimilar protein's primary (ie, amino acid sequence) and higher-order structures (ie, secondary, tertiary, and quaternary) are analyzed. The enzymatic post-translational modifications (eg, glycosylation, phosphorylation), potential variations (eg,

oxidation), and intentional chemical modifications (eg, PEGylation sites) of the protein are additionally assessed.

For structural and functional comparison, the structure of the biosimilar is closely compared with that of the reference product. The biosimilar then undergoes additional functional comparative testing to ensure that its biological activity, potency, and mechanism of action are highly similar to those of the reference biologic.

5.7.4 Module 4: Non Clinical Study

5.8: Non-clinical study considerations

Summary of non-clinical study considerations	Stepwise approach. Analytical studies and *in vitro* pharmaco-toxicological studies to be conducted first and decision is made as to what the extent of what, if any, *in vivo* work in animal studies will be required. Following approach recommended to be tailored to the concerned product on a case-by-case basis. Step 1: *In vitro* studies ↓ Step 2: Determination of need for *in vivo* studies ↓ Step 3: *In vivo* studies
	Step 1: *In vitro* studies Studies should include relevant assays on: -Binding to target(s)known to be involved in the pharmaco-toxicological effects and/or pharmacokinetics of the reference product -Signal transduction and functional activity /viability of cells known to be of relevance for the pharmaco-toxicological effects of the reference product. *Since *in vitro* assays may often be more specific and sensitive to detect differences between the biosimilar and the reference product than studies in animals, these assays can be considered as paramount for the non-clinical biosimilar comparability exercise
	Step 2: Determination of need for *in vivo* studies Following factors are to be considered when the need for *in vivo* non-clinical studies is required (but not limited to): -Presence of potentially relevant quality attributes that have not been detected in the reference product (e.g. new post-translational modification structures).

	-Presence of potentially relevant quantitative differences in quality attributes between the biosimilar and the reference product. -Relevant differences in formulation, e.g. use of excipients not widely used for biotechnology-derived proteins. *Although each of the factors mentioned above do not necessarily warrant *in vivo* testing, these issues should be considered together to assess the level of concern and whether there is a need for *in vivo* testing.
	Step 3: *In vivo* studies -PK and PD of the biosimilar and the reference product should be quantitatively compared (if model allows) -Although immunogenicity assessment in animals is generally not predictive for immunogenicity in humans, it may be needed for interpretation of *in vivo* studies in animals. Therefore, blood samples should be taken and stored for future evaluations of pharmacokinetic/toxicokinetic data if then needed. -Studies regarding safety pharmacology, reproduction toxicology, and carcinogenicity are not required for non-clinical testing of biosimilars. - Studies on local tolerance are usually not required. However, if excipients are introduced for which there is no or little experience with the intended clinical route of administration, local tolerance may need to be evaluated. If other *in vivo* studies are performed, evaluation of local tolerance may be part of the design of that study instead of the performance of separate local tolerance studies.
Uganda	√
EU	√
South Africa	√
U.S.A	√
WHO	√

*The symbol "↓" shows the stepwise approach in establishing biosimilarity. Requirements at a stage must be fulfilled before proceeding to the next.

The non-clinical, also known as pre- clinical principles required for establishing biosimilarity are the same across the selected jurisdictions including Uganda, although as mentioned for the quality attributes, the EU and U.S.A guidelines provide in-depth information and explanation of the various principles. The Ugandan guideline provides reference to the EU and ICH guidelines for more detailed information.

Preclinical studies involve comparison of *in vivo* pharmacology (PK and PD), toxicology, and immune response. A comparison of nonclinical PK and PD may be useful in reducing residual uncertainty

regarding similarity, and such a study may be conducted as a comparative single-dose study or incorporated into a single preclinical toxicity study if appropriate. Immunogenicity may also be evaluated in animal studies; results may aid in detection of differences between the proposed biosimilar and reference product as opposed to predicting clinical similarity in immunogenicity69.

5.7.5 Module 5: Clinical study

Table 5.9: Clinical study considerations

Description of clinical study considerations	It is recommended to generate the clinical data required for the biosimilar comparability exercise with the biosimilar product derived from the commercial manufacturing process and therefore representing the quality profile of the batches to become commercialized. (Any deviation to be justified and supported by adequate bridging data). The clinical biosimilar comparability exercise is a stepwise approach, as follows: PK (and PD, if feasible) Clinical efficacy and safety trial(s), (or, in certain cases, confirmatory PK/PD studies for demonstrating clinical biosimilar comparability) Summary of clinical studies to be performed: a) PK* b) PD (if feasible)* c) Clinical efficacy of the biosimilar and reference product (study designs and efficacy endpoints specified). d) Clinical safety (comparative safety data), immunogenicity testing (in a comparative manner to the reference product) * In certain cases, comparative PK/PD studies may be sufficient to demonstrate clinical comparability of the biosimilar and the reference medicinal product, provided that the following conditions are met: • The selected PD marker/biomarker is an accepted surrogate marker and can be related to patient outcome to the extent that demonstration of similar effect on the PD marker will ensure a similar effect on the clinical outcome. • There may be PD-markers that are not established surrogates for efficacy but are relevant for the pharmacological action of the active substance and a clear dose-response or a concentration-response relationship has been demonstrated. In this case, a single or multiple dose-exposure-response study at two or more dose levels may be sufficient to waive a clinical efficacy study.
Uganda	√
EU	√
South Africa	√
U.S.A	√

WHO	√

The clinical principles required for establishing biosimilarity are the same across the selected jurisdictions including Uganda. As mentioned for the quality, and non-clinical attributes, the EU and

U.S.A guidelines provide in-depth information and explanation of the various principles. The Ugandan guideline provides reference to the EU and ICH guidelines for more detailed information.

The goal of the clinical development program for a biosimilar is to demonstrate the absence of any clinically meaningful difference relative to the reference molecule. The extent of the clinical program depends on the degree of similarity demonstrated in preclinical testing, including structural, functional, and animal studies. Clinical studies include human pharmacology studies (PK and PD), efficacy and safety, immunogenicity and extrapolation.[69]

5.7.5.1 Pharmacovigilance

Table 5.10: Pharmacovigilance requirement

	Uganda	EU	South Africa	U.S.A	WHO
Requirement for close monitoring of the clinical safety of a biosimilar in all approved indications and a continued benefit-risk assessment in the post-marketing phase	√	√	√	√	√

All selected jurisdictions including Uganda recommend a comprehensive pharmacovigilance plan to be submitted as part of the marketing authorization application, taking into account immunogenicity risks identified during product development as well as any anticipated future risks (RMP).

5.7.5.1.1 Risk Management Plan (RMP)

Table 5.11: Requirement for RMP

	Uganda	EU	South Africa	U.S.A	WHO
Requirement for RMP at the time of submission of the marketing authorization application	√ To be submitted along with a Periodic Benefit-Risk Evaluation Report (PBRER), in accordance with principles of pharmacovigilance planning found in relevant guidelines such as ICH E2E.	√ Marketing authorization applications should include a description of the pharmacovigilance system and RMP in accordance with EU legislation and pharmacovigilance guidelines.	√ Applicant should present a pharmacovigilance plan/risk management plan with the registration application, according to the SAHPRA guidelines. RMP should be in place (or planned) for the biosimilar at the time of application. It may be necessary to include South African and special population groups in RMP activities.	X Unlike the mandatory RMP in the EU, South Africa, WHO and Uganda; the U.S has a Risk Evaluation and Mitigation Strategies (REMS) program.* REMS programs are created by the sponsor at the request of the FDA, either pre-or post-approval[76].	√ Manufacturer is required to submit a safety specification and pharmacovigilance plan (RMP) at the time of submission of the marketing authorization application, in accordance with principles of pharmacovigilance planning found in relevant guidelines such as ICH E2E.

√ - Yes/available

X – No/not available

*According to information on the U.S. FDA website, a Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication. While all medications have labeling that informs health care stakeholders about medication risks, only a few medications require a REMS.

REMS are not designed to mitigate all the adverse events of a medication, these are communicated to health care providers in the medication's prescribing information. Rather, REMS focus on preventing, monitoring and/or managing a specific serious risk by informing, educating and/or reinforcing actions to reduce the frequency and/or severity of the event.

According to the WHO guideline for the biosimilars pilot project[57], a risk management plan is a detailed description of the activities that continuously ensure patients' safety and their benefit from a medicinal ingredient. A risk management plan includes:

- safety specifications, which summarize the known and potential safety issues and missing information about the rDNA-derived biotherapeutic;
- a pharmacovigilance plan to further evaluate important known or potential safety concerns and to provide post-marketing data where relevant information is missing;
- a risk minimization plan, which provides proposals on how to minimize any identified or potential safety risk.

With the exception of the U.S.A with a non-mandatory REMS program at the time of submission of marketing authorization application, all other jurisdictions including Uganda require submission of a RMP at the time of submission of the marketing authorization application.

Uganda's proposed guideline has an additional requirement for a PBRER at the time of submission of the marketing authorization application. However, according to the ICH guideline E2C70, the main objective of a PBRER is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile. It is a post-marketing approval requirement and not a pre-marketing requirement as proposed in the guideline. It is recommended that this requirement is removed as pre-market requirement and included as a post-market requirement in addition to post-marketing safety commitments such as targeted questionnaires, phase IV studies, registries, and specialized follow-up for long-term use[71].

It is also recommended that a reference or link to the existing Ugandan pharmacovigilance requirements is included, such as the *Guidelines on submitting periodic safety update report and other reports that may be relevant to determine the safety, efficacy and quality of a drug, April 2018*, available on the NDA website: www.nda.or.ug.

5.8 Other guideline related documents: Summary Information for Similar Biotherapeutic Product (Appendix 2)

It is stated under section 2.1 of the proposed guideline that a template of the Summary Information for Similar Biotherapeutic Product (SIB) is attached as appendix 2 of the guideline. General information of the components SIB template is intended to be filled out by the MAH while NDA will fill out the components which are general for the product summary including the status of the registered product. The SIB will be filled out with the dossier of first authorization. For any amendment, SIB will be updated. The purpose of the SIB was not mentioned. Although the title suggests that SIB contains summary information of the biosimilar, this is not clearly stated.

WHO published a Quality Information Summary template (QIS) for medicines on its website[72]. It is stated that the QIS provides an accurate record of technical data in the product dossier (PD) at the time of prequalification and thereafter serves as an official reference document during GMP inspections, variation assessments and requalification assessments as performed by WHO. It represents the final, agreed upon key information from the PD review[73]. This information is included in the WHO QIS template covering forward and may serve as a guide for drafting the purpose of the proposed SIB.

However, Appendix 2 of the proposed guideline contains a template of the Public Assessment Summary Information for Similar Biotherapeutic Product and not a SIB template as stated. The format and content of the Public Assessment Summary Information for Similar Biotherapeutic Product appended is the same as that of the Public Assessment Summary Information for Biosimilars (PASIB) published by the IPRP Biosimilar Working Group (IPRP-BWG) [37]. According to the IPRP website, the PASIB template is intended to assist National Regulatory Authorities (NRAs) in making available a summary of the assessment (review) of biosimilar applications in their jurisdiction / country in a common language, for example, in English. For NRAs who already publish assessment reports following the review of medicinal product applications in their country, these are often in the local language and as a result are

not easily accessible to the wider (global) community. The PASIB is intended to increase transparency and to facilitate the transition from a local assessment report to one prepared in the English language. The PASIB includes key information and summarized details of the biosimilar review. The template and its use were designed to reduce local translation effort by the NRA to a minimum and should be completed in accordance with local requirements, however, if found to be helpful the applicant / sponsor for the biosimilar can populate data elements of the document in English, as part of the process37. Therefore, in order to avoid confusion, the PASIB should be removed and a SIB attached as appendix 2. In drafting a SIB, the PASIB template may provide useful information for inclusion in the SIB as applicable to the Ugandan situation. For example, the PASIB requires inclusion of information on interchangeability and extrapolation of indications, areas for which the proposed biosimilar guideline is not clear.

5.9 Other principles

5.9.1 Policy on interchangeability

Table 5.12: Statements on interchangeability

Uganda	EU	South Africa	U.S.A	WHO
Interchangeability, substitution and switching are defined in the proposed guideline but are not addressed anywhere else in the guideline. NDA's position on interchangeability is unknown.	EMA does not regulate interchangeability, switching and substitution of a reference medicine by its biosimilar. These fall within the remit of EU Member States	Biosimilars are not considered to be interchangeable with the reference medicine or other medicines of the same class. Substitution in terms of Section 22F (Generic substitution) of Act 101 of 1965 (i.e. the practice by with a different product to that specified on the prescription is dispensed to the patient without the prior informed consent of the treating physician) does not apply to Biosimilars.	In U.S.A, a biosimilar may be substituted for the reference product without intervention of the health care provider who prescribed the reference product. However, general scientific issues relating to the demonstration on interchangeability are not included in the reviewed guidelines are addressed separately on the U.S. FDA website.	Not applicable. It is stated that important issues associated with the use of SBPs including interchangeability and substitution of RBP with SBP, need to be defined by NRAs and are therefore not elaborated in the guideline.

Of all the jurisdictions reviewed, only USA has a policy on interchangeability with respect to biosimilars and reference products. According to information on the page *Biosimilar and Interchangeable Products* on the U.S FDA website74, an interchangeable product is a biosimilar product that meets additional requirements outlined by the Biologics Price Competition and Innovation Act. As part of fulfilling these additional requirements, information is needed to show that an interchangeable product is expected to produce the same clinical result as the reference product in any given patient. Also, for products administered to a patient more than once, the risk in terms of safety and reduced efficacy of switching back and forth between an interchangeable product and a reference product has to be evaluated. An interchangeable product may be substituted for the reference product without the involvement of the prescriber. FDA's high standards for approval are expected to assure health care providers that they can be confident in the safety and effectiveness of an interchangeable product, just as they would be for an FDA-approved reference product[74].

The proposed biosimilar guideline does not mention NDA's position on interchangeability and/or substitution. This position needs to be clearly stated in the guideline. A clear definitive policy on interchangeability will ensure better outcomes for patients without placing inordinate burden on health care professionals.

5.9.2 Possibility of extrapolation of efficacy and safety from one therapeutic indication to another

Table 5.13: Statements on extrapolation of efficacy and safety from one indication to another

Uganda	EU	South Africa	U.S.A	WHO
No clear statement on extrapolation of biosimilar from one indication to another. Reference made to WHO guideline.	If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate justification. Extrapolation should be considered in the light of the	Where the clinical effects of the medicine have been shown to be related to the same mode of actions and the safety and efficacy of the biosimilar medicine and the reference product have been demonstrated for a particular clinical	If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity,	If similarity between the SBP and the RBP has been convincingly demonstrated, and if the manufacturer can provide scientific justification for such extrapolation, the SBP may be approved for use in other clinical indications for which the

	totality of data, i.e. quality, non-clinical and clinical data. Extrapolation of immunogenicity from the studied indication /route of administration to other uses of the reference product should be justified.	indication, it may be possible to extrapolate these data to other indications of the reference product that have not been independently and specifically studied for the biosimilar medicine in clinical trials. The applicant should provide convincing motivation and in detail discuss the scientific basis and the risk/benefit for the proposed extrapolated clinical indications. Safety and immunogenicity of the biosimilar product must be sufficiently characterized.	and potency in an appropriate condition of use, the applicant may seek licensure of the proposed product for one or more additional conditions of use for which the reference product is licensed. However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.	RBP is used but which have not directly been tested in clinical trials. Any significant differences between the SBP and the chosen RBP detected during the comparability exercise would indicate that the products are not similar and that more extensive nonclinical and clinical data may be required to support the application for licensing.

With the exception of Uganda, guidelines from all the jurisdictions provide for extrapolation of clinical data across indications with sufficient scientific justification for extrapolating clinical data to support determination of biosimilarity for each condition of use for which marketing authorization is sought. The U.S.A guidelines on Scientific considerations in Demonstrating Biosimilarity to a Reference Product, give examples of such scientific justification.

The proposed NDA biosimilar guideline lacks a clear statement on extrapolation of biosimilar from one indication to another. It is instead stated that the WHO guideline should be consulted for further guidance on extrapolation. It is however considered important that information on extrapolation is provided in the guideline including examples of scientific justification that may be provided as in the U.S.FDA guideline. For further information, the reflection paper prepared by the IPRF Biosimilars

Working Group (BWG) is a useful document for understanding the current thinking of various regulatory authorities of different regions with respect to the extrapolation of indications from reference product to the biosimilar during the development of these products[75].

Chapter Six: Conclusion and recommendations

In general, the findings reveal that the proposed Uganda biosimilar guidelines are comparable with those from the chosen jurisdictions, i.e. the EU, South Africa, U.S.A and WHO, with respect to the technical principles required in establishing biosimilarity; quality, non-clinical and clinical requirements. All the guidelines from the five (5) jurisdictions recommend a stepwise approach in establishing biosimilarity. They require a comprehensive comparison of the quality attributes of the biosimilar and reference products. Fulfilment of this requirement then determines the need and amount of additional studies required i.e. non-clinical and clinical studies. A risk-based approach is used to evaluate all data and information in support of the biosimilarity of the proposed product. It was however noted that specifically the EU and U.S.A guidelines provide detailed information on the biosimilarity approach in comparison to the other jurisdictions. The types of studies at each step are specified in detail. In addition, the clinically meaningful differences that would lead to rejection of biosimilar applications are defined. In addition to the technical assessment requirements, all guidelines from selected jurisdictions and the proposed Uganda guideline recommend a comprehensive pharmacovigilance plan to be submitted as part of the marketing authorization application.

The selected jurisdictions have clearly stated positions on reference product requirements including origin and sourcing; interchangeability and/or substitution; and on the possibility of extrapolation of efficacy and safety from one therapeutic indication to another. However, Uganda's position is not stated in the guideline. This should be included in the guideline.

The general guideline review also revealed a number of inconsistencies which were highlighted and recommendations for revision and/or improvement made. A comprehensive list of recommendations to

NDA, Uganda, for inclusion in the proposed guidelines is included as Annexure I. A copy of the same was shared with NDA by email on 01 March 2019.

In conclusion, the proposed biosimilar assessment guideline with revisions will go a long way in ensuring that Uganda's NDA effectively regulates these products to ensure that safe, efficacious and good quality biosimilars are available on the market. They will also serve as a starting point in increasing public and health care provider confidence in these products. The proposed assessment guidelines are comparable with those from the selected jurisdictions with respect to the key technical assessment principles. These should be finalized with recommended revisions and made available, for example, on the NDA website.

In future, it would be of value to review the process of developing scientific guidelines at NDA. Guidelines are key documents with a huge potential to prevent access to quality medicines if not developed according to international standards. Also, the available resources and capacity, including competence, for biosimilars regulation in Uganda can be assessed to identify gaps and make recommendations aimed at ensuring a strong and effective biosimilars regulatory system.

Annexes

Annex I: Recommendations

Annex II: Research Permission (separately provided)

Annex III: NDA Uganda – Draft Biosimilar Guidelines (separately provided)

Annex IV: Project proposal (separately provided)

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Appendix I: Recommendation

1.0 Recommendations: Guideline update

Guideline section	Finding	Recommendation
Table of contents	"2.2 Considerations For The Choice Of Rbp"	Proposed revision: 2.2 Consideration for the choice of RBP
Glossary of Terms (0.3)	Terms **Genetic engineering** and **in-process control** are defined but not included in guideline body	Review documents used for guideline preparation and consider inclusion or exclusion, as appropriate
	Bioequivalence: "Two proprietary preparations of a drug, when administered in the same dose and by the same route, will have the same bioavailability, duration of action and efficacy" The term bioavailability was not defined	To consider adoption of the WHO definition as follows: "Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of rate (Cmax and tmax) and extent of absorption (area under the curve), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same."
	Biotherapeutics: "Therapeutic biological products, some of which are produced by recombinant DNA technology" The terms biological products and recombinant DNA technology are used and also mentioned in the guideline but were not defined	**Biological products/medicines:** **South Africa** All medicines that contain a living organism, or are derived from a living organism or biological processes are considered Biological Medicines. They include, but are not limited to the following: v. Plasma-derived and animal products, e.g. Clotting factors, Immunosera, Antivenoms vi. Vaccines vii. Biotechnology-derived medicines (rDNA products) e.g. rHu-antihaemophilic factors, hormones, cytokines, enzymes, monoclonal antibodies, erythropoietins, nucleic acids; viii. Products developed for Human Gene therapy.

		U.S.A Virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. **Proposed:** Consider adopting any of the above or a combination of the two, e.g., "All products that contain a living organism, or are derived from a living organism or biological processes, applicable to the prevention, treatment, or cure of a disease or condition of human beings are considered biological products. These include viruses, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound)" **<u>Recombinant DNA technology</u>** Consider adoption of the EU definition; "Technology that involves combining sequences of DNA that do not occur naturally, for example inserting a gene for producing a therapeutic protein"
	Comparability Exercise: "Activities including study design, conduct of studies, and evaluation of data, that are	EU and WHO definitions are more comprehensive. Either of these may be adopted. EU:

	designed to investigate whether the products are comparable (head to head comparison)"	Head-to-head comparison of a biosimilar with its reference medicine to rule out any significant differences between them in terms of structure and function. This scientific principle is routinely used when a change is introduced to the manufacturing process of medicines made by biotechnology, to ensure that the change does not alter safety and efficacy. WHO: Head-to-head comparison of a biotherapeutic product with a licensed originator product with the goal of establishing similarity in quality, safety and efficacy. Products should be compared in the same study using the same procedures.
	ICH: "Means International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. For more information, see http://www.ich.org/."	According to the ICH website, the ICH membership has grown and the list of observers increased: https://www.ich.org/about/members-observers.html **Proposed:** NDA to update definition in line with current information on the ICH website. Alternatively, the definition may be deleted from the glossary of terms and instead included in the list of abbreviations, with a link to the website. This will ensure that the ICH related information in the guideline is up to date.
The Concept of Similar Biotherapeutic Products (1.1)		Statements in the EU and U.S.A guidelines provide detailed information on the biosimilarity approach, and may be adopted. The types of studies are specified at each step, and differences considered to be clinically meaningful are defined.
Considerations for the	WHO text was fully adopted. However this	**Proposed:**

choice of RBP (2.2)	was not adapted to the Ugandan situation/domesticated	"The RBP should be registered in Uganda or by a stringent regulatory agency (SRA) or a regulatory agency that NDA aligns itself with; and should have been marketed for a suitable duration and have a volume of marketed use such that the demonstration of similarity to it brings into relevance a substantial body of acceptable data regarding the safety and efficacy." The definition of an SRA has evolved over the years; however the following WHO interim definition may be used: • a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; or • an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or • a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015). Information on sourcing of the RBP should be included the guideline. The following obtained from the WHO PQP website, for comparator products used in bioequivalence study may be used for guidance: "To prove the origin of the comparator product, the applicant must include the following documents in the product dossier submitted for evaluation; • copy of the RBP labelling which should include: the name of the product; name and address of the manufacturer; batch number; and expiry date (clearly visible on the labelling)

		• copy of the invoice from the distributor or company from which the RBP was purchased; the address of the distributor must be clearly visible on the invoice • documentation verifying the method of shipment and storage conditions of the RBP from the time of purchase to the time of study initiation • a statement — by the company executive responsible for the application for registration certifying the authenticity of the above documents and that the RBP was purchased from the specified national market."
Manufacturer's declaration (2.4.1)	It was stated that…. "applicants intending to develop SBPs should meet with regulators in their country of origin to present their product development plans and establish a schedule of milestones that will serve as standards for future discussions with the respective regulators"	**Proposed:** To draft a guidance document(s) for pre-submission meetings and preferably publish on the NDA website. The following documents/information may be used for guidance: • U.S.FDA (Formal Meetings Between the FDA and Sponsors or Applicants of Bs UFA Products; Guidance for Industry; Draft Guidance, June 2018,) • EMA Pre-authorisation guidance; EMA • WHO Pre-submission meetings; WHO Prequalification • TGA Pre-submission meetings with TGA
Quality (module 3), Non-clinical (module 4) and Clinical considerations (module 5)		Develop a system of regularly checking references stated to ensure that they are current. Information on EMA, U.S. FDA, ICH and WHO websites is regularly updated including guidelines. NDA should also consider providing detailed information as is the case with the EU and U.S.A. This may be provided as appendices to the main guideline. This will not only provide readily accessible information to the applicants during product development and clarity on information to be submitted in the application, but will also provide information for capacity

		building of Uganda's biosimilar assessors.
Pharmacovigilance (5.6) /Risk Management Plan (RMP)	Proposed guideline has an additional requirement for a **PBRER** at the time of submission of the marketing authorization application. However, according to the ICH guideline E2C, the main objective of a PBRER is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile. It is a post-marketing approval requirement and not a pre-marketing requirement as proposed in the guideline.	It is recommended that this requirement is removed as pre-market requirement and included as a post-market requirement in addition to post-marketing safety commitments such as targeted questionnaires, phase IV studies, registries, and specialized follow-up for long-term use, if considered feasible (taking into consideration available resources)
		It is also recommended that a reference or link to the existing Uganda pharmacovigilance requirements is included, such as the *Guidelines on submitting periodic safety update report and other reports that may be relevant to determine the safety, efficacy and quality of a drug, April 2018*, available on the NDA website: www.nda.or.ug.
Appendix2: Summary Information for Similar Biotherapeutic Product (SIB) template	The purpose of the SIB was not mentioned in section 2.1	**Proposed:** Information in the WHO QIS template covering forward may be used for drafting the purpose. It is also stated that the QIS provides an accurate record of technical data in the product dossier (PD) at the time of prequalification and thereafter serves as an official reference document during the course of GMP inspections, variation assessments and requalification assessments as performed by WHO. It represents the final, agreed upon key information from the PD review.
	Appendix 2 of the proposed guideline contains	In order to avoid confusion, the PASIB should be removed

	a template of the Public Assessment Summary Information for Similar Biotherapeutic Product and not a SIB template as stated. The format and content of the Public Assessment Summary Information for Similar Biotherapeutic Product appended is the same as that of the Public Assessment Summary Information for Biosimilars (PASIB) published by the IPRP Biosimilar Working Group (IPRP-BWG). According to the IPRP website, the PASIB template is intended to assist National Regulatory Authorities (NRAs) in making available a summary of the assessment (review) of biosimilar applications in their jurisdiction / country in a common language, for example, in English. For NRAs who already publish assessment reports following the review of medicinal product applications in their country, these are often in the local language and as a result are not easily accessible to the wider (global) community. The PASIB is intended to increase transparency and to facilitate the transition from a local assessment report to one prepared in the English language. The PASIB includes key information and summarized details of the biosimilar review. The template and it's use were designed to reduce local translation effort by the NRA to a minimum and should be completed in accordance with local requirements, however, if found to be helpful the applicant / sponsor for the biosimilar can populate data elements of the document in	and a SIB attached as appendix 2. In drafting a SIB, the PASIB template may provide useful information for inclusion in the SIB as applicable to Uganda's situation. For example, the PASIB requires inclusion of information on interchangeability and extrapolation of indications, areas that are not clear in the proposed biosimilar guideline.

	English, as part of the process.	

a) Formal Meetings Between the FDA and Sponsors or Applicants of Bs UFA Products; Guidance for Industry; Draft Guidance, June 2018, U.S.FDA, accessed on 28/02/19 https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM609662.pdf?utm_campaign=FDA%20Issues%20Draft%20Guidance%20for%20Industry%3A%20Formal%20Meetings%20Between%20the%20Food%20and%20Drug%20Administration&utm_medium=email&utm_source=Eloqua

b) Pre-authorisation guidance; EMA; accessed on 28/02/19 https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pre-authorisation-guidance

c) Pre-submission meetings with TGA, March 2018, accessed on 28/02/19 https://www.tga.gov.au/publication/pre-submission-meetings-tga

d) Pre-submission meetings; WHO Prequalification, accessed on 28/02/19 https://extranet.who.int/prequal/search?search_api_views_fulltext=presubmission&op=search

e) WHO QIS Template, July 2017, accessed on 01/03/19 https://extranet.who.int/prequal/key-resources/documents/Q

f) The International Pharmaceutical Regulators Forum website, accessed on 01/03/19 https://www.i-p-r-f.org

1.1 Recommendations: Other

A. The proposed guideline should be finalized as soon as possible and made available on the NDA website.

B. **Policy on interchangeability and/or substitution**

The proposed biosimilar guidelines should clearly state NDA's position on interchangeability and/or substitution. A clear definitive policy on interchangeability will ensure better outcomes for patients without placing inordinate burden on health care professionals. Below are the statements on interchangeability in the reviewed guidelines.

Uganda	EU	South Africa	U.S.A	WHO
Interchangeability, substitution and switching are defined in the proposed guideline	EMA does not regulate interchangeability, switching and substitution of a reference medicine by its biosimilar. These fall within the remit of EU	Biosimilars are not considered to be interchangeable with the reference medicine or other medicines of the same class.	In U.S.A, a biosimilar may be substituted for the reference product without intervention of the health care provider who	Not applicable. It is stated that important issues associated with the use of SBPs including

but are not addressed anywhere else in the guideline. NDA's position on interchangeability is unknown.	Member States	Substitution in terms of Section 22F (Generic substitution) of Act 101 of 1965 (i.e. the practice by with a different product to that specified on the prescription is dispensed to the patient without the prior informed consent of the treating physician) does not apply to Biosimilars.	prescribed the reference product. However, general scientific issues relating to the demonstration on interchangeability are not included in the reviewed guidelines are addressed separately on the U.S. FDA website.	interchangeability and substitution of RBP with SBP, need to be defined by NRAs and are therefore not elaborated in the guideline.

C. **Possibility of extrapolation of efficacy and safety from one therapeutic indication to another**

The proposed NDA biosimilar guideline should include information on extrapolation as intended to be addressed by NDA and not only include a reference WHO guideline. The U.S. FDA guidelines provide useful information on examples of scientific justification that may be provided. Also, the reflection paper prepared by the IPRF Biosimilars Working Group (BWG)* is a useful document in understanding the current thinking of various regulatory authorities of different regions with respect to the extrapolation of indications from reference product to the biosimilar during the development of these products. Below are the statements from reviewed guidelines.

Uganda	EU	South Africa	U.S.A	WHO
No clear statement on extrapolation of biosimilar from one indication to another. Reference made to WHO guideline.	If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate justification. Extrapolation should be considered in the light of the totality of data, i.e. quality,	Where the clinical effects of the medicine have been shown to be related to the same mode of actions and the safety and efficacy of the biosimilar medicine and the reference product have been demonstrated for a particular clinical indication, it may be	If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an	If similarity between the SBP and the RBP has been convincingly demonstrated, and if the manufacturer can provide scientific justification for such extrapolation, the SBP may be approved for use in other clinical indications for which the RBP is used but which

	non-clinical and clinical data. Extrapolation of immunogenicity from the studied indication /route of administration to other uses of the reference product should be justified.	possible to extrapolate these data to other indications of the reference product that have not been independently and specifically studied for the biosimilar medicine in clinical trials. The applicant should provide convincing motivation and in detail discuss the scientific basis and the risk/benefit for the proposed extrapolated clinical indications. Safety and immunogenicity of the biosimilar product must be sufficiently characterized.	appropriate condition of use, the applicant may seek licensure of the proposed product for one or more additional conditions of use for which the reference product is licensed. However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.	have not directly been tested in clinical trials. Any significant differences between the SBP and the chosen RBP detected during the comparability exercise would indicate that the products are not similar and that more extensive nonclinical and clinical data may be required to support the application for licensing.

*IPRP Biosimilars Working Group, June 16 2017; Reflection Paper on extrapolation of Indications in Authorization of Biosimilar Products, available at http://www.iprp.global/page/biosimilar-activities

D. NDA website should include a separate list of registered biotherapeutic medicines and biosimilar products. Currently information on approved biotherapeutics and biosimilars is not readily accessible. Alternatively, the current online drug register may be revised to provide for therapeutic and product class.

E. NDA should consider drafting information for patients and health care providers about biosimilars in order to increase their understanding of these products and confidence in them. The EMA and U.S.FDA websites have detailed information intended to increase understanding of these products and build confidence.

   a. In order to increase biosimilar uptake, it is stated in the WHO bulletin Kang et al (2018) that regulatory authorities should make an effort to communicate with, and educate, all

stakeholders, including patients, about biosimilars and their approval. The provision of such information contributes to better transparency and increase public trust in biosimilars.

WHO bulletin; Hye-Na Kang & Ivana Knexevic; 2018; Regulatory evaluation of biosimilars throughout their product life-cycle; accessed on 26/02/19 http://www.who.int/bulletin/volumes/96/4/17-206284/en/

Patient and health care provider biosimilar information on the EMA website:

EMA has not only published guidance and guidelines for biosimilar manufacturers/developers, but has also published information for patients and health care professionals to improve understanding of biosimilar medicines in the EU. The following information for patients and health care professionals is currently published:

- An animated video for patients explaining key facts on biosimilar medicines and how EMA works to ensure that they are safe and effective as their reference biological medicines. The video is currently available in the following European languages: Dutch, English, French, German, Italian, Polish, Portuguese and Spanish.
- An information guide for patients published by the European Commission explaining what biosimilar medicines are, how they are developed and approved in the EU and what patients can expect in terms of availability and safety. The guide is available in 23 official EU languages.
- Biosimilars in the EU – Information guide for health care professionals. The guide is available in eight (8) languages; English, Dutch, French, German, Italian, Polish, Portuguese and Spanish.

In addition, the EU publishes summaries of the European public assessment reports (EPARs) for each of the approved biosimilars. The reports explain how EMA assessed the medicine to recommend its authorization in the EU and its conditions of use. Product information which provides practical information for health care providers and patients is also published for each approved biosimilar. The product information includes summary of product characteristics, labelling information and package insert or patient information leaflet (PIL).

(EMA website: Biosimilar medicines: Overview; https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview)

Patient and health care provider biosimilar information on the U.S.FDA website

U.S.FDA published a Biosimilars Action Plan (BAP) to provide information about the key actions the agency is taking to encourage innovation and competition among biologics and the development of biosimilars.

Also, through its Center of Drug Evaluation and Research (CDER), the FDA offers a variety of patient and prescriber outreach materials including:

a) videos [The Promise of Biosimilars, The Basics of Biosimilars, The Concept of Interchangeability, The Biosimilar Development Process, and Analytical Data for Biosimilar Products];
b) Fact sheets [Biological Product Definitions, Biosimilar Product Regulatory Review and Approval, Prescribing Biosimilar Products, and Prescribing Interchangeable Products]; Infographics [Biosimilar Development Process, and What is a Biosimilar];
c) stakeholder toolkit intended to help stakeholders promote FDA as a resource for information on biosimilars and interchangeable products and to encourage prescribers and patients to talk to each other about these medicines. The stakeholder kit includes: animated GIFs, website badges, print Ads, infocards, twitter posts and facebook/LinkedIn posts.

The website also includes drop-in content e.g. newsletter articles for prescribers and patients related to biosimilars.

The FDA offers online courses, webinars and presentations (FDA staff presentations) to help manufactures, the public and regulators worldwide learn more about biologics, biosimilars and interchangeable products. Product information, that is, prescribing information and any other related information e.g. press releases is available for each of the approved biosimilar medicines.

(U.S.FDA website: Biosimilars; https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/default.htm)