WHO standards for biotherapeutics, including biosimilars: an example of the evaluation of complex biological products

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The most advanced regulatory processes for complex biological products have been put in place in many countries to provide appropriate regulatory oversight of biotherapeutic products in general, and similar biotherapeutics in particular. This process is still ongoing and requires regular updates to national regulatory requirements in line with scientific developments and up-to-date standards. For this purpose, strong knowledge of and expertise in evaluating biotherapeutics in general and similar biotherapeutic products, also called biosimilars, in particular is essential. Here, we discuss the World Health Organization’s international standard-setting role in the regulatory evaluation of recombinant DNA–derived biotherapeutic products, including biosimilars, and provide examples that may serve as models for moving forward with nonbiological complex medicinal products. A number of scientific challenges and regulatory considerations imposed by the advent of biosimilars are described, together with the lessons learned, to stimulate future discussions on this topic. In addition, the experiences of facilitating the implementation of guiding principles for evaluation of similar biotherapeutic products into regulatory and manufacturers’ practices in various countries over the past 10 years are briefly explained, with the aim of promoting further developments and regulatory convergence of complex biological and nonbiological products.

Keywords: biotherapeutics; biosimilars; complex biological products; national regulatory authorities; WHO standards

Introduction

Biologics, referred to as biologics in some countries, are the prime example of complex medicinal products. However, there are also nonbiological complex products, such as iron–carbohydrate drugs, liposomal drugs, glatiramoids, and, most recently, nanomedicines, and discussions are currently ongoing regarding the regulatory oversight of all these medicines and especially their subsequent or follow-on versions, as exemplified by a meeting held at the New York Academy of Sciences in November 2016.1 While the regulatory pathway for authorization of generic versions of small molecule drugs has been well established, guidance on the regulatory oversight of complex drug products is still evolving. The most advanced regulatory processes for complex drug products have been put in place in many countries to provide appropriate regulatory oversight of biotherapeutics (BTPs) in general and similar BTP products (SBPs) in particular. The World Health Organization (WHO) has been actively involved in this work and in promoting global convergence of regulatory approaches to assure the quality, safety, and efficacy of SBPs at the global level. We discuss the WHO’s international standard-setting activities in the field of biologicals, and in particular for BTPs and biosimilars, which may serve as models for moving forward with nonbiological complex drugs.

Although the WHO is not a regulatory authority, it has, as part of its mandate, a unique role to support regulatory authorities in its 194 member states. More precisely, one of the WHO core functions is...
“setting norms and standards and promoting and monitoring their implementation.” The WHO has been much involved in setting and promoting global standards for biologicals since it was established in 1948. Indeed, the need for global standardization of biological medicines was recognized early in the 20th century, and international biological standardization and the provision of International (measurement) Standards were established under the League of Nations through its Commission on Biological Standardization. The Expert Committee on Biological Standardization (ECBS) was established in 1947 and ever since has been active in establishing WHO standards for biologicals.

The development and promotion of international standards is part of the WHO constitution and, in the early 1960s, was extended to include written standards for biological substances in the form of guidelines and recommendations. These take a global perspective and are published in the WHO Technical Report Series. Originally focused on vaccines, the role of the international recommendations or guidelines for biological substances was to ensure the availability of vaccines of appropriate quality for use in international immunization programs. Furthermore, these documents serve as a benchmark for global acceptability of these products and as a basis for defining national regulatory requirements for licensing as well as for postlicensure evaluation. These activities developed into the present WHO’s Norms and Standards Programme for biologicals, which includes both measurement (physical standards) and written standards for vaccines, BTPs, including biosimilars, and other biologicals, intended as guidance for national regulatory authorities (NRAs) and manufacturers. The development of measurement standards involves elaborate collaborative studies in numerous laboratories worldwide, and the WHO written standards are based on scientific consensus achieved through considerable international consultation. The work is supported by WHO collaborating centers, NRAs in many countries, pharmacopoeias, manufacturers associations, and academia. The WHO also plays an important role in the implementation of new guidelines and recommendations. Detailed information about WHO international standards for biologicals can be found at the WHO biologicals website (http://www.who.int/biologicals/publications/trs/en).

In May 2014, the Sixty-seventh World Health Assembly adopted two relevant resolutions: one promoting access to BTP products and ensuring their quality, safety, and efficacy and the other on regulatory system strengthening, in which the WHO was requested to provide guidance, especially on dealing with increasingly complex BTP products, including SBPs. In that context, a number of activities were conducted to assist WHO member states in strengthening their expertise and capacity for evaluation of biosimilars, improving regulatory convergence, and using existing resources in a better way. Some of these activities are described in the following sections as a review of examples and challenges that may facilitate regulatory preparedness for complex medicinal products.

Science-based evaluation of biotherapeutic products

In the past 30 years, developments in molecular biology have enabled genes encoding natural biologically active proteins to be identified, modified, and transferred from one organism to another in order to obtain highly efficient synthesis of their products. This has led to the production of biological medicines prepared by recombinant DNA (rDNA) technology using a range of different expression systems, such as bacteria, yeast, transformed cell lines of mammalian origin, insect and plant cells, and transgenic animals and whole plants. Recombinant DNA technology is also used to produce biologically active proteins that do not exist in nature, such as chimeric, humanized, or fully human monoclonal antibodies (mAbs) or antibody-related proteins or other engineered biological medicines, such as fusion proteins. There has also been great progress since the early days of biotechnology in the ability to purify biologically active macromolecules, and especially in the analytical techniques used for their characterization. Therefore, the protein, lipid, and carbohydrate components of biological macromolecules can now be characterized in great detail. Even so, it is still not possible to fully predict the biological properties and clinical performance of these biological macromolecules on the basis of their physicochemical characteristics alone.

Regulatory measures were put in place by the major regulatory agencies very early on in the development of rDNA-derived products, and they were regulated as biologicals. BTP products differ
Table 1. Major differences between small molecule drugs and biotherapeutic products

| Small molecule chemical drugs | Biotherapeutics |
|------------------------------|----------------|
| ■ Produced by predictable chemical processes. | ■ Produced in living cells, which are inherently variable systems. Difficult to control. Viral safety validation essential for mammalian cells. |
| ■ Usually well-defined low-molecular-weight molecules. | ■ Complex high-molecular-weight molecules with higher-order structures. Biological properties usually highly sensitive to external factors. |
| ■ Relatively easy to characterize completely, both main product and contaminants. | ■ Difficult to characterize. Sophisticated up-to-date analytical methods needed. Drug substance defined by the manufacturing process. |
| ■ Biological methods are rarely used in product characterization. | ■ Rely on biological test methods (bioassays) to characterize product (e.g., activity (potency), immunogenicity, and safety). Bioassays are inherently variable and standardization is essential. |
| ■ Usually nonimmunogenic. | ■ Can be immunogenic with varying clinical consequences, from none to serious. |

from small molecule drugs in many important ways (Table 1). In addition to the difficulty of fully predicting clinical performance from physicochemical characterization alone, the production processes, as well as the bioassays used to measure their activities, are biological systems known to be inherently variable. This feature has important implications for the safety and efficacy of the resulting product. Therefore, a prerequisite for introducing such biological substances into routine clinical use is the need to ensure consistency of quality from lot to lot, and for this purpose robust manufacturing and quality-control processes, many of which are in-process controls, are essential. Consistency is critical, since slight changes can lead to major adverse effects of the product, such as immunogenicity, with potentially serious clinical implications.

As with many other new technologies, a new set of safety issues for consideration by both industry and regulators was generated by these biotechnologies. Potential safety concerns arose from the novel processes used in manufacture, from product- and process-related impurities, and from the complex structural and biological properties of the products themselves. Factors that have received particular attention include the possible presence of contaminating oncogenic host-cell DNA in products derived from transformed mammalian cells, as well as the presence of adventitious viruses. Since the nature and manufacturing of these products are highly sophisticated, they require similarly sophisticated laboratory techniques and standards to ensure their proper control. Although comprehensive analytical characterization of the drug substance and drug product is expected, considerable emphasis is also given to the manufacturing process (i.e., to process validation and in-process control). Adequate control measures relating to the starting materials and manufacturing process are as important as analysis of the drug product itself. Thus, data on the host-cell quality, purity, freedom from adventitious agents, adequate in-process testing during production, and effectiveness of test methods are required for licensing.

In terms of clinical evaluation, it is well known that rDNA-derived BTPs may induce unwanted immune responses in recipients. Immunogenicity of rDNA-derived BTPs should therefore always be investigated before authorization. Since animal data are usually not predictive of the immune response in humans, immunogenicity needs to be investigated in the target population. The frequency and type of product antibodies induced against the active substance, impurity, or excipient, as well as possible clinical consequences of the immune response, should be thoroughly assessed.

The immune response against a BTP is influenced by many factors, such as the nature of the drug substance, product- and process-related impurities (e.g., host-cell proteins and aggregates), excipients and stability of the product, the route of administration (subcutaneous administration is usually more immunogenic than intravenous administration), the dosing regimen (intermittent
use is usually more immunogenic than continuous use), and patient-related, disease-related, and/or therapy-related factors (e.g., antibody development is more likely in an immunocompetent than in an immunosuppressed state). The consequences of unwanted immunogenicity on safety may vary considerably, ranging from clinically irrelevant to serious and life-threatening (e.g., serious infusion/anaphylactic) reactions. Neutralizing antibodies may directly alter the pharmacodynamic effect of a product (i.e., by blocking the active site of the protein), leading to the reduction or loss of efficacy. Binding antibodies often affect pharmacokinetics and may indirectly influence pharmacodynamics. Thus, an altered effect of the product over time owing to antidrug antibody formation might be a composite of pharmacokinetic, pharmacodynamic, and safety effects.

Regulatory guidelines on the quality, safety, and efficacy of rDNA-derived biotherapeutic proteins

At a very early stage in the development of rDNA-derived medicines, the European Medicines Agency (EMA) and the United States Food and Drug Administration produced guidelines and points to consider, respectively, for the development and evaluation of these new products. Such guidelines, based as they were on long experience with traditional biological substances, set the scene for regulatory expectations for both clinical trials and licensing. At the global level, the WHO produced a series of guidance documents on the quality, safety, and efficacy of rDNA-derived products, including specific guidance for products such as interferons and mAbs. These regulatory concepts have been instrumental in establishing expectations for the quality, safety, and efficacy of rDNA-derived BTPs.

More up-to-date guidance has been developed since that time. There are two basic WHO documents that have replaced the earlier guidelines: one deals with evaluating the quality, safety, and efficacy of rDNA-derived products, including specific guidance for products such as interferons and mAbs. Together, they cover the major issues regarding the development, manufacture, and evaluation of rDNA-derived BTPs that distinguish biological medicines from small molecule chemical drugs.

In 2015, regulatory assessment of approved rDNA-derived BTPs was addressed in an addendum to the above-mentioned guidelines for BTP protein products prepared by rDNA technology. The main focus of the above-mentioned document adopted by the ECBS in 2015 was regulatory assessment to address situations where, for various reasons, BTP protein products prepared by rDNA technology were licensed with data packages that did not follow current international regulatory standards for these biologicals. This includes, for example, BTP products licensed via a generic pathway or with limited analytical, nonclinical, and/or clinical data.

Most recently, the WHO was asked to develop guidelines on procedures and data requirements for changes to approved BTP products, including biosimilars. Regulation of changes to approved BTP products is critical to ensuring that products of consistent quality, safety, and efficacy are distributed after licensure. Consultation on that topic has been initiated, and a face-to-face discussion took place in Seoul, the Republic of Korea on April 27–28, 2017. The new guidelines are expected to emphasize the importance of appropriate regulatory oversight during the entire life cycle of BTPs, including biosimilars. This guidance document will be posted on the WHO biologics website for another round of public consultation from July to September 2017 and submitted to the ECBS for consideration and advice in October 2017.

Challenges imposed by the arrival of similar biotherapeutic products

Recombinant DNA–derived BTP products now form an increasingly important component of global health care and have a highly successful record of treating many life-threatening and chronic diseases. Unfortunately, their cost has often been high, and they represent an increasing proportion of healthcare expenditure. This has limited their accessibility to patients, especially in developing countries. However, the expiry of patents and/or data protection for the first originator’s BTPs has ushered in an era of products that are designed to be copies of licensed originator products, and these were expected to be more affordable, since it was thought that their licensing would rely partly on prior information.

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These are the so-called SBPs or biosimilars. A variety of terms, such as “follow-on protein products” and “subsequent-entry biologics” have also been coined to describe these products. There has been considerable global interest in this development, but also some difficult and contentious issues to resolve. These relate not only to science but also to regulatory processes and to legal aspects of patent and data protection. The key question was how to handle the licensing of these products if relying, in part, on data from the innovator product.

An important issue for the scientific community is to recognize that development and regulatory evaluation as well as the use of SBPs require a very good understanding of BTP products in general and the concept of biosimilarity in particular. The expertise in regulatory evaluation of these products is essential for assuring quality, safety and efficacy during the entire life of a product. The problem that many WHO member states faced with the arrival of biosimilars was lack of the expertise for evaluation of BTPs in general. It is likely that the same scenario may happen with complex nonbiological drugs. Therefore, lessons learned in various countries will be elaborated below, with the intention of facilitating discussion among regulators and developers of nonbiologic complex drugs.

In parallel with the arrival of biosimilars, there were also noninnovative biological products developed as copy products and licensed through generic pathways, as described below. They may cause problems, and thus appropriate regulatory oversight of these products is of paramount importance.

Guidelines on the evaluation of similar biotherapeutic products

The EMA was the first regulatory authority to tackle the problem of licensing and subsequently developed BTPs. In 2004, it developed the concept of similar biological medicinal products, popularly shortened to biosimilars, and in 2005 it developed a regulatory framework and guidelines for dealing with them. This involved a comparability exercise that relied on a head-to-head demonstration of the similarity of the new product’s characteristics (physicochemical and biological activity) to a chosen licensed reference biological product (RBP), which, providing similarity was shown, could lead to a reduced nonclinical and clinical data package. This would still include some head-to-head clinical comparisons, including immunogenicity, with the same reference product.

Considerable international consultation led by the WHO evaluated how best to deal with biosimilars at the global level. This led to a better understanding of the challenges in the regulatory evaluation of the quality, safety, and efficacy of biosimilars, to an exchange of information between regulators, and to the identification of key issues and gaps. It became clear that there was, globally, a wide range of experience, not only in dealing with the new biosimilars, but also in dealing with rDNA-derived BTP products in general, and that there was a need for a regulatory global road map. At the International Conference of Drug Regulatory Authorities (ICDRA) (Seoul, 2006), the WHO was requested to develop a global regulatory consensus and guidance on the evolving topic of biosimilars, and the following years saw a number of WHO consultations on the regulatory evaluation of biosimilars, involving regulators, manufacturers, academics, and other experts. An important point of agreement globally was that biosimilars do not meet the “identical” criteria of true generics and should not be regulated under generic (small molecule) drug regulations. BTP products are by nature not identical. However, there was also agreement on the possibility of licensing a new biological medicinal product on the basis of its similarity to a well-established licensed originator product. This would involve extensive comparative product characterization (quality) with a licensed comparator product and, provided that the quality data showed biosimilarity, a reduced nonclinical and clinical data package would be appropriate. However, this package would still be a comparative exercise. Following further extensive international consultation over a number of years, the WHO guidelines on the evaluation of similar biotherapeutic products were adopted by the WHO ECBS in October 2009.

The WHO guidelines take a stepwise approach to the demonstration of similarity. Reliance is placed on the head-to-head demonstration of similarity of new product characteristics (physicochemical/biological activity) to a chosen licensed reference product to justify a reduced nonclinical and clinical data package. The demonstration of similarity of the SBP to the RBP in terms of quality attributes is a
prerequisite for the reduction of the nonclinical and clinical data set required for licensing. The head-to-head comparability exercise, with the same reference product throughout, applies not only to quality but also to nonclinical and clinical aspects, and the guidelines emphasize the need to employ testing strategies that are sensitive enough to detect any relevant differences between the new product and the RBP. In particular, the WHO guidelines point out that the clinical studies should be designed specifically to demonstrate comparable safety and efficacy between the two products using well-established clinical models and, preferably, equivalence rather than noninferiority designs, and not just to establish the overall safety and efficacy profile of the new product, which is already established by the RBP. The aim of clinical comparability study for biosimilars is solely to show that the reference product and potential biosimilar are comparable clinically. These studies are not intended to show clinical efficacy and safety, since these aspects were already demonstrated for the reference product. Comparability of the immunogenicity of the new and reference products is an essential aspect. Such targeted studies would be expected to be smaller than normal clinical trials and therefore less expensive and time-consuming to undertake. Overall, the decision to approve a product as a biosimilar relies on the totality of evidence—biosimilarity in all three attributes, quality, nonclinical, and clinical. Some RBPs have more than one therapeutic indication, but the abridged clinical studies will generally have studied only one. When similarity between the new product and the reference has been demonstrated in one therapeutic indication, extrapolation to other indications may be possible, provided that certain conditions are met. However, this should not be automatic and must be justified.

The set of globally acceptable key principles outlined above for the regulatory evaluation and licensing of SBPs has served well as a basis for setting national requirements for SBPs.

The WHO Expert Committee recommended that issues subject to particular national situations be excluded from the guidelines. These include but are not limited to (1) intellectual property issues, (2) interchangeability and substitutability of SBPs with RBPs, and (3) labeling and prescribing information. The ECBS also recommended that the WHO plays an active role in facilitating the implementation of the principles outlined in the document into regulatory and manufacturers’ practice worldwide.

The development of mAbs as SBPs raised some additional issues. Because mAbs are a major class of rDNA-derived products that have achieved outstanding success in treating many life-threatening and chronic diseases, a lot of attention was paid to these products. Because of the structural complexity and heterogeneity of mAbs, including posttranslational modifications, the quality attributes of mAbs can vary from product to product. Furthermore, one mAb product may have multiple indications. Therefore, biosimilar comparability studies between a candidate biosimilar mAb and a reference product mAb are challenging for both developers and regulators. Consequently, the WHO was requested to take into account the technological advances in the characterization of rDNA-derived products, and particularly mAbs. In response, WHO organized informal consultations in 2015 and 2016 on the evaluation of quality, safety, and efficacy of SBPs containing mAbs. The outcome of these discussions led to the development of WHO guidelines on the evaluation of mAbs as SBPs, which was adopted by the ECBS in 2016.

Implementation of WHO guidelines: experience in various countries

The WHO Guidelines on the evaluation of similar biotherapeutic products (2009) are intended to provide a globally acceptable set of basic principles for licensing biosimilars and to serve as a basis for setting national licensing requirements. It was recognized from the beginning that the guidelines would not by themselves resolve all issues, and they leave space for NRAs to formulate more specific requirements to take account of, for example, national legal constraints. Since the adoption of the WHO guidelines by the ECBS in 2009, several WHO implementation workshops have been held (Fig. 1) to discuss the WHO guidelines and to air outstanding issues with regulators and manufacturers from more than 50 countries. Regulators in WHO member states are playing a pivotal role in implementing WHO guiding principles in their national regulations. The WHO is facilitating that process by organizing implementation workshops with lectures, case studies, and reviews of examples that serve as opportunities to discuss scientific
as well as practical aspects in a forum of regulators, manufacturers, and academia. The key lectures, outcomes of the discussions, and reports from countries have been published (28 articles in a special issue of *Biologicals* (39, 2011)), including very useful case studies (Table 2). These discussions indicate considerable convergence in approach to biosimilars but also, where national guidelines on biosimilars have been developed, highlight some differences in details between jurisdictions. Examples of differences include requirements for the choice of RBP and the extent of extrapolation of indications allowed from an abridged set of clinical studies. Usually, the RBP chosen for the comparability exercise of a biosimilar is one licensed in the jurisdiction concerned. However, the acceptability of an RBP that is not licensed by the NRA but is licensed in another country (a so-called “foreign RBP”) is a reasonable approach for the regulatory authorities of countries with a small market for RBPs, and the WHO guidelines are flexible in this respect. At the time of adoption of WHO SBP guidelines, the EMA required the RBP (reference medicinal product according to EMA terminology) to be already licensed in the European Union. That was considered a very strict approach. Later, the EMA also introduced a flexible approach with well-defined conditions for using a foreign RBP to facilitate global development of biosimilars. The benefit of using nationally licensed RBPs is that data supporting the clinical performance and other data, including safety, will be readily available to the NRA. On the other hand, the use of a foreign RBP requires well-defined criteria for its acceptability and for the reliability of the NRA where the product is licensed. Some countries have established a list of recognized NRAs as a basis for considering products licensed by these authorities as potential candidates for RBPs. This is a sort of unilateral recognition that may work well in certain countries. Some jurisdictions have questioned the need for the direct head-to-head comparability studies in terms of quality and nonclinical and clinical performance and favor some alternative regulatory pathways. Nevertheless, at the WHO consultations in Seoul in 2010 and in Geneva in 2015, it was reaffirmed that only medicinal products authorized on the basis of a full head-to-head comparability package involving quality and nonclinical and clinical aspects should be called biosimilars (or SBPs, subsequent-entry biologics, and follow-on biologics). Copy products licensed by other pathways would need to be called by another name.
Table 2. Overview of WHO implementation workshops on BTPs, including SBPs

| Implementation workshop | First SBP (global) | Second SBP (global) | Third SBP (global) | First BTP (global) | First BTP/SBP for African countries (regional) |
|-------------------------|-------------------|---------------------|-------------------|-------------------|-----------------------------------------------|
| When                    | August 2010       | May 2012            | May 2014          | September 2015    | Ghana FDA                                     |
| Host                    | MFDS              | NIFDC               | MFDS              | Ghana             | Ghana                                         |
| Where                   | Korea             | China               | Korea             | Ghana             |                                               |
| Participants            | Regulators from 11 countries + industry | Regulators from 16 countries + industry | Regulators from 23 countries + industry | Regulators from 16 countries + industry |                                               |
| Main topic for case study practice | Clinical study design: equivalence versus noninferiority | Quality assessment of mAbs | Efficacy study design on mAbs | Immunogenicity assessment of mAbs | Quality assessment of EPO |
| Publications            | Special issue: *Biologicals 39*, 2011, with 28 articles including meeting report | *Biologicals 42*, 2014 | *Biologicals 43*, 2015 | *Biologicals 43*, 2015 | Meeting report WHO biological web site, 2016 (http://www.who.int/biologicals/areas/biological_therapeutics/) |
| Lectures                | Statistical considerations for confirmatory clinical trials for SBPs | Immuno- gensity assessment of biotherapeutic products: an overview of assays and their utility |                                               |                                               |                                               |
| Case studies            | Comparing equivalence and noninferiority approaches | The role of the quality assessment (of mAbs) in the determination of overall biosimilarity | Efficacy study design and extrapolation: infliximab and rituximab | Assessment of unwanted immunogenicity of mAbs: TNF antagonist and CD20 mAbs | Evaluation of quality attributes (EPOs) and understanding of structure–function relationships |

One of the difficulties in the context of regulatory evaluation of SBPs was the appropriate use of WHO measurement (physical standards) for BTP products. Although it was clearly stated in the guidelines on SBPs\(^1\) that international or national measurement standards and reference reagents are not intended for use as RBPs during the comparability exercise, there were some expectations that these standards might serve as RBPs. This misunderstanding was clarified during the implementation workshops, and the intended use of these standards was elaborated in a review article published in a special issue of the journal *Biologicals* in 2011.\(^4\)

During implementation workshop discussions, it also became clear that some rDNA-derived BTP products, as well as copy products, had been licensed by certain NRAs using data packages that did not follow current international standards, even for the rDNA-derived medicinal products. Sometimes, a range of different products were on the market in these countries at the same time, and the question was raised as to what should be done with these already licensed products. This situation was discussed at the ICDRA meeting held in Singapore in 2010, and the WHO was requested to develop guidance on risk management strategies for “copy” BTPs already licensed using generic pathways. The WHO responded by developing guidelines on the regulatory assessment of rDNA-derived BTPs in cases where their licensing did not follow current international regulatory standards, including, for example, BTP products licensed via a generic pathway or with limited analytical, nonclinical, and/or clinical data. These guidelines were adopted in 2015\(^1\) and specifically address regulatory expectations for rDNA-derived BTPs, including SBPs, the review of

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*Note: The table and text content are presented in a readable format, with the table structure and content accurately transcribed from the image.
products already on the market, and the stepwise regulatory assessment and actions to be considered following assessment. The stepwise regulatory assessment approach outlined was designed to offer flexibility and to promote the accessibility of BTP products of assured quality, safety, and efficacy. A number of countries have introduced new regulations for BTPs/biosimilars in recent years, and these include provision to reassess products approved before the adoption of new regulations. The value of the WHO guidelines is in a comprehensive consultation process that takes into account different views and perspectives while making a consensus for the most appropriate approach for global development of these products. The document emphasizes the need for regulatory oversight throughout the life cycle of a product and recommends an early dialogue between regulators and manufacturers to assure quality, safety, and efficacy of these products in the interest of patients who need them most.

**Lessons learned with complex biological products, such as biotherapeutics, including biosimilars**

In many countries, BTP products did not have proper recognition until biosimilars were developed and submitted for licensing. With the arrival of biosimilars, a need for well-defined regulation of BTPs was seen as a basis for formulating additional requirements for SBPs. During the consultations with regulators, manufacturers, academics, medical doctors, pharmacists, patients, and other relevant parties, many issues were discussed, and some of the lessons learned are summarized below.

One of the challenges that regulators in developing countries face is related to the understanding of the concept of biosimilarity. It is important to recognize that biosimilar products are BTPs by nature, which means that the same principles that apply to BTPs also apply to SBPs. There is therefore a need to have a very good understanding of BTP products before reviewing biosimilars. In addition, expertise and experience are critical for dealing with specific issues, such as a stepwise approach in the evaluation of these products, a concept of comparability studies in terms of quality, nonclinical, and clinical evaluation, including the use of RBPs, extrapolation of indications, and the interpretation of data from these studies. This is one of the major challenges in building capacity in developing countries. Both prelicensure and postlicensure evaluation and the entire regulatory oversight are of critical importance to assure quality, safety, and efficacy of these products. These issues may also impose a problem for evaluation of nonbiological complex drugs.

Another challenge is the regulatory oversight of products that have not been licensed by any fully functional (competent) regulatory authority before being submitted to NRAs in developing countries. In such cases, regulators in developing countries become “a first entry point” for these products, usually with limited expertise and experience, and they usually seek some help from the WHO or from other NRAs. In particular, a number of questions regarding product-specific issues are raised during prelicensure as well as the postlicensure evaluation of these products, and the decision-making process is usually very difficult. In addition, it is often a missed opportunity for defining postmarketing commitment by the manufacturers to monitor safety and effectiveness of these products in the population.

The evaluation and licensing of complex products in the absence of appropriate national regulatory frameworks for these products is a quite challenging issue for regulators, but also for manufacturers and developers of biosimilar products. When national regulatory requirements become available, reevaluation of the products already on the market is deemed necessary. This requires regulatory actions and a solid mechanism to require additional data when needed. For example, a number of growth hormones, erythropoietin products, insulins, and mAbs were developed after the originators were licensed, but before regulation for biosimilars came into place. Many of them were licensed as “biogenerics” without clinical data and with limited or no comparability data with the originator. After establishing regulation for biosimilars, it would be expected that manufacturers submit comparability data in order to maintain marketing authorization according to up-to-date regulation for biosimilars. Therefore, it is important to establish an approach for regulatory risk assessment, as described in the WHO document, and to ensure enforcement mechanisms and a regular update of that approach. In that context, the role of regulators in ensuring quality, safety, and efficacy of BTP products on the market, on one hand, and an adequate response from manufacturers in generating
and submitting relevant data, on the other hand, are two critical aspects for increasing confidence in biosimilar products.

Communication and transparency of regulatory processes, requirements, and the basis of regulatory decisions are some of the critical elements for building trust in biosimilar products. The WHO encourages regulators to publish their national requirements and assessment reports and to clearly communicate regulatory expectations in order to pave the path for manufacturers to generate an appropriate set of data to assure the quality, safety, and efficacy of biosimilars. Through collaboration with the Biosimilar Working Group of the International Pharmaceutical Regulators Forum, the WHO contributed to the preparation of the “Public Assessment Summary Information,” with the aim of improving regulatory convergence. As part of implementation workshops, establishing regulatory networks at the global, regional, and international levels was recognized as an opportunity for information sharing. However, work sharing proved more difficult to establish. In particular, the roles and responsibilities, limitations in terms of confidentiality agreements regarding the product-specific information, and complexity in the decision-making process were some of the issues that made a work-sharing approach much more demanding than information sharing. Networking among manufacturers has also promoted discussions on biosimilars at the global and regional levels.

Finally, better information and education for medical doctors, prescribers of biosimilars, and patients and other stakeholders (e.g., pricing committees and insurance companies) is essential to relay information regarding the concept of biosimilarity and associated issues and assure the appropriate use of biosimilars. In many cases, biosimilars have not been prescribed owing to a perception that these products are “copy” products and not as good as the originators. This is one of the most common misunderstandings that created a barrier to the use of biosimilars. The WHO, as well as many other organizations and bodies, has provided some materials, such as FAQs (http://www.who.int/biologicals/biotherapeutics/en/), to explain some basic facts regarding the biosimilars, but it seems that there is still a need to do more to educate key players.

For complex nonbiologic products, it is important to assess current regulatory frameworks for evaluation of these products at the global level, identify gaps, and prepare an action plan for strengthening regulatory oversight before and after licensure of these products. Discussions organized by the New York Academy of Sciences in 2012 and 20161,2 and others34–5 have provided a lot of insight into the problems, but further discussions, particularly with regulators in developing countries, are very much needed. Most likely, some of the issues described as challenges for SBPs would also raise a number of questions regarding the evaluation of nonbiological complex drugs. In addition, there may be some issues that have not been addressed in the context of biosimilars but need to be discussed to assure quality, safety, and efficacy of complex nonbiologic drugs.

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Competing interests

The authors declare no competing interests.

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