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Policy considerations for originator and similar biotherapeutic products

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Biotherapeutic products (BTPs), also known as biotherapeutic medicines, contain structurally complex active substances produced by living organisms. Due to their complexity and method of manufacture BTPs require distinct regulatory approval standards relative to chemically-synthesized small molecule medicines. This is also relevant for licensing copied versions of a BTP, or similar biotherapeutic products (SBPs) made by a different manufacturer where regulatory concepts developed for generics should not have been applied. In all these licensing scenarios regulators need to evaluate the results of comparability exercises, including sensitive head-to-head analytical, pre-clinical and clinical comparisons with the original product as a basis for approval.

SBPs do not contain chemically identical active substances, and may have slightly different benefit-risk profiles, therefore it is necessary to monitor post-approval safety on a product-specific basis. Policymakers may therefore emphasize the need for product-specific identification in patient records and safety reports using either a unique trade name or a distinguishable non-proprietary naming system. The unique nature of BTPs also informs the nature and degree of interchangeability between the originator and SBPs versions. Many policymakers also emphasize that switching between SBPs should only occur with the involvement of the prescriber. It is recommended that pharmacy substitution would only be appropriate when there is a robust framework for a competent authority to assess product-specific evidence of interchangeability. Another challenge is posed by the historical existence in some jurisdictions of copy BTPs that were not assessed according to current regulatory standards. To address this situation the World Health Organization has proposed a regulatory assessment framework wherein the status of such products can be normalized via the orderly submission and review of supplementary data.

Keywords: Biosimilar, biologic, comparability, similarity, manufacturing, non-proprietary names, interchangeability, substitution, pharmacovigilance

1. Introduction

Biotherapeutic products (BTPs) are medicines whose active substances are or are derived from proteins (such as growth hormone, insulin, antibodies) and other substances, and are produced by living organisms (such as cells, yeast and bacteria). They are larger and more complex than chemically-synthesized small molecule

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Table 1
Unique complexity of biotherapeutic products (BTPs)

	Chemically-synthesized small molecule medicines	BTP
Starting materials	Chemicals	Living organisms (cell lines)
Raw materials	Chemicals	Complex media
Manufacture	Chemical synthesis followed by relatively simple purification	Cell culture followed by relatively difficult purification
Active substance characteristics	Low Molecular Weight (typically $<$ 1000 Da)	High Molecular Weight (typically $>$ 10,000 Da)
	Single, high purity molecular entity	Complex, heterogeneous mixture of product-related substances
	Fully characterized	Partially characterized
	Relatively stable	Relatively labile

medicines, and their characteristics and properties are typically dependent on their source living organism and manufacturing process. This complexity makes the full characterization of BTPs particularly difficult. Chemically-synthesized small molecule medicines are instead medicines whose active ingredients are produced through a step-by-step chemical synthesis process. They are derived from structurally simple chemical compounds with smaller molecular weight compared to BTPs. Therefore, BTPs cannot be copied like small molecule drug products because of their complexity (see Table 1).

A similar biotherapeutic product (SBP) is defined as a product that is similar to an already authorized originator biotherapeutic product, with demonstrated similarity to the latter in terms of quality, efficacy and safety assessed through direct (head-to-head) comparisons. SBPs are also referred to as biosimilars, follow-on biologics, and subsequent entry biologics.

In 2006, the European Medicines Agency (EMA) was one of the first regulatory authorities to develop guidelines and create standards for licensing SBP [1]. The World Health Organization (WHO) published its "Guidelines for the evaluation of similar biotherapeutic products" in 2009 [2].

They were closely followed by Canada [3] and the United States (US) [4] guidance in 2010 and 2015 respectively. Many other national regulatory authorities (NRAs) also have developed national regulatory pathways for SBP registration encouraged by the WHO document.

2. Similarity as a distinct concept from generic identity of active ingredient

As their name implies, SBPs are "similar" but not identical versions of their innovative reference biotherapeutic product (RBP). Whereas producing generic versions of off-patent chemically-synthesized medicines is relatively easy – it involves copying a stable chemically-synthesized molecule with a single identifiable structure – producing an SBP is far more complicated due to the complex molecular structure

and the unique manufacturing process required for BTPs. Indeed, unlike chemically-synthesized medicines, it is impossible for SBPs to be exact copies of the RBP. It is important to note that using terms "biogenerics" or "generic biologicals" for SBPs is incorrect simply because it isn't possible to directly recreate the same molecule.

3. Manufacturing changes in complex proteins

BTPs, being made using living systems, are more sensitive to changes in manufacturing and handling conditions than are small molecule medicines made using relatively straightforward chemical synthesis processes. The quality attributes of a BTP are determined by a wide range of factors, which include the active substance manufacturing process as well as the drug product formulation and fill-finish steps. Small changes in manufacturing can therefore alter the final product. The high complexity of this process requires precision, conformance to good manufacturing practices and defined specifications in order to maintain the safety and efficacy of the product over time. Over 250 in-process tests are carried out for a BTP, compared to around the 50 done for a chemically-synthesized small molecule medicine [5].

Medicinal products are manufactured by a diversity of techniques and processing steps, which depend on the unique molecular characteristics of the product. During the life-cycle of a product, manufacturing process changes or other changes to the approved medicinal product are frequently needed for many reasons, including to: a) make the production process more efficient or the product more pure, at higher yields or with higher quality; b) increase manufacturing capacity (scale-up); c) move the production into a new or different facility (ensuring continuous supply); d) incorporate technical or scientific progress (e.g., improved analytical methods); e) implement changes that are consequential to changes made by suppliers of active substances, excipients, raw materials or packaging materials; f) comply with new regulatory requirements; and g) supply the medicinal product in a new dosage strength, delivery device, or under a new formulation.

Enabling development and post-approval changes is the use of comparability exercises evaluating before and after samples for any significant protein profile differences that may predict different safety and efficacy outcomes.

4. BTPs comparability/SBPs similarity exercises for evaluating manufacturing changes

4.1. Comparability exercises for changes by the same manufacturer

Comparability is the exercise that will demonstrate that pre-change and post-change versions of a product have a similar profile in terms of quality, safety, and efficacy [6,7]. ICH Q5E restates that comparable does not mean identical [8]. "The

demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product."

The extensiveness of the comparability exercise can depend on the step of the process where the change is being introduced, plus the nature and number of changes being implemented. Comparability exercises often rely on the incremental nature of a given change and are supported by historical experience with the product and process to inform a risk-based assessment. Process-related data plus the post-change product quality attributes and impurities are compared to an extensive history of process and product knowledge by the same manufacturer. A critical element of the exercise is the analytical assessment in which post-change samples, enough to represent the consistency of the change, are compared in side-by-side assays with samples representing the pre-change process.

Many times the analytical assessment of the change is enough to establish the comparability of the product. When residual uncertainty remains and the analytical assessment is insufficient to establish comparability then preclinical and/or clinical evaluation may be necessary. The essence of the comparability exercise is that process-related, analytical and any additional comparisons should demonstrate that the post-change process continues to be representative of the clinical trial material used to establish the safety and efficacy of the product.

4.2. Similarity exercises for abbreviated development of SBPs

A SBP will most likely have differences in manufacturing processes, raw materials and equipment relative to its RBP. The "similarity" exercise is adapted from the concepts developed for the same-manufacturer comparability exercise, but differs in the balance of risk and required evidence. The manufacturer, lacking knowledge of the RBP manufacturing details, must therefore rely on comprehensive testing including analytical, non-clinical and clinical studies to establish comparability/biosimilarity. The incorporation of similarity exercises to regulate SBPs is vital to ensure that the quality, safety and efficacy are highly similar to those of the innovator RBP. This risk-assessment process must ensure that there are no clinically meaningful differences with the RBP before the SBP receives marketing authorization, thus minimizing risks to patients.

SBP similarity exercises rely on a foundation of structural and functional studies including tailored preclinical and clinical programs which should be considered a sequential process.

"The scientific principles underlying the comparability exercise required for changes in the manufacturing process of a given BTP and for the development of a SBP are the same. Even so, data requirements for the latter are higher and, at least in the EU, always include clinical studies because, due to the completely independent

manufacturing processes, some differences between the SBP and the RBP can be expected, and the potential impact of these differences on safety and efficacy cannot be predicted from analytical assessment alone…" [9].

Regulatory decisions have to take all the comparative data into account evaluating each step to determine the extent of uncertainty to be addressed by the next step in the program. This assessment is done through a stepwise exercise, the main objective of which is to demonstrate biosimilarity. These exercises start with a comparison of the quality characteristics of the intended SBP against those of the RBP utilizing a suitable set of sensitive assays covering physicochemical and biological properties. Routine and extended characterization tests are normally used in these exercises which may include stability and degradative studies.

Once high similarity is demonstrated at the quality level, the assessment continues with comparative targeted pre-clinical and clinical studies utilizing relevant and sensitive assay systems, patient populations and clinical endpoints having the intention to exclude relevant differences in the safety (including immunogenicity) and efficacy profile of the SBP compared to the RBP. This means that patients can expect a comparable clinical profile between the two medicines.

4.3. Ongoing life-cycle management for RBPs and SBPs

After receiving a marketing authorization an SBP sponsor may seek to make post-approval changes that should be assessed using the above-mentioned "same manufacturer" comparability framework. Such post-approval comparability assessments for either the SBP or the RBP should demonstrate that significant changes have not taken place impacting clinical safety and efficacy performance thus avoiding product divergence and concerns over biosimilar designation [9].

5. Regulatory and policy challenges

5.1. Overview of assessments

A comprehensive similarity exercise is required to ensure the safety and efficacy of SBPs, which should thus be regulated via pathways that are distinct from those applied to generic medicines.

SBPs must be evaluated on the basis of a rigorous regulatory pathway to ensure that they demonstrate high similarity in quality, safety, and efficacy to an approved RBP. The RBP should be carefully selected to ensure that it has been licensed on the basis of a full dossier and that its benefit risk profile is well established. As outlined in the preceding section the biosimilar regulatory pathway should require the sponsor to provide evidence of similarity from a stepwise similarity exercise. That exercise should include comparative analytical characterization of the proposed SBP and an appropriate RBP and comparative non-clinical and clinical studies.

Regulators will recognize that even comprehensive analytical characterization using state-of-the-art technology may not identify all differences between a proposed SBP and the RBP. When analytical studies reveal differences it may be challenging for sponsors and regulators to assess their clinical relevance. Therefore, uncertainties regarding the biosimilarity and the clinical implications of differences found will remain and must be investigated through additional comparative pre-clinical and clinical studies.

Immunogenicity in human subjects/patients cannot be predicted from analytical and non-clinical studies, and immunogenicity profiles may differ between the SBP and RBP. Thus, it is important for the sponsor to develop and qualify sensitive and robust immunogenicity assays and to provide a comprehensive comparison of clinical immunogenicity. Clinical comparability studies are typically limited in scope and duration, so a more complete assessment of the SBP's benefit-risk profile with respect to immunogenicity may require post-marketing experience. Regulators should take these points into consideration in evaluating the evidence from the clinical comparability studies and the proposed risk management plan for the SBP.

Finally, given the complexity and sensitivity of BTPs and the fact that products from different manufacturers may differ in subtle fashion that might impact their benefit-risk profile, a robust pharmacovigilance system is a key component of a science-based regulatory pathway for all BTPs, including SBPs.

Some considerations for regulatory systems to enable a robust SBP regulatory framework [10]:

1) Establish a regulatory framework that is distinct from that for generic chemically-synthesized small molecule medicines.
2) Require that sponsors of the SBP select an appropriate RBP approved on the basis of a complete dossier for use in comparative studies.
3) Require that the proposed SBP and the RBP can be demonstrated to share the same mechanism of action (to the extent known), dosage form, strength, and route of administration.
4) Require that sponsors of SBPs demonstrate a comprehensive understanding of the physicochemical and biological characteristics of the SBP and RBP through thorough comparative analytical studies.
5) Require sponsors of SBPs to confirm high similarity of the proposed SBP to the RBP in terms of safety and efficacy through appropriately designed tailored non-clinical and clinical studies.
6) Require that immunogenicity of the proposed SBP be adequately evaluated (i.e. in an appropriate number of patients to permit the detection of differences in the types and rates of immunogenic events) pre-market and also appropriately evaluated post-market, and compared to that of the RBP.
7) Provide for mechanisms to ensure clear prescribing, dispensing, use and pharmacovigilance of SBPs once marketed (e.g., clear labeling, unique identifiers, patient and physician education, and an appropriate pharmacovigilance plan).

5.2. Non-proprietary naming

BTPs have never quite followed the traditional drug naming paradigm of using the active ingredient's international non-proprietary name (INN) [11,12]. Although several non-glycosylated biotherapeutic classes (e.g., insulins or somatropins) have shared INNs, many glycosylated biotherapeutics (e.g., epoetins, follitropins) have INNs with unique Greek letter suffixes. These distinguishable INNs are determined according to WHO's policy that applies a distinguishable Greek letter suffix to the INN for each new version of a glycosylated biotherapeutic [13]. This policy is based on the assumption that glycoproteins manufactured using fundamentally different cell substrates and culture processes will likely have unique glycosylation patterns. A second distinction is that versions of BTPs have typically (but not always) been marketed using proprietary trade names, departing from the common generic drug labeling convention.

The development of SBPs has stimulated policy debates regarding whether to apply the generic drug naming paradigm or to apply a modified approach. The generic drug naming paradigm might encourage the perception by patients and prescribers that SBPs have identical active substances and could therefore be used interchangeably with the originator product. Published surveys provide evidence that some prescribers may make such inferences [14]. Furthermore, prescriptions using the INN instead of a brand name might be fulfilled at the pharmacy using any version of the product. Such "generic prescribing" is encouraged for chemical drugs. These perceptions and practices might therefore promote higher utilization of SBPs, much as they do for generic drugs.

However, some policy makers recognized that policies and practices used for generic drugs might conflict with safe prescribing and use of BTPs. Versions of BTPs are not considered to have identical active substances and may not be fully interchangeable at the individual patient level. Many jurisdictions encourage prescribers to be involved in decisions to prescribe a specific version of a BTP, and prescribing by INN is discouraged. Finally, it is generally agreed that post-marketing safety surveillance for BTPs should be tracked and analyzed at the individual product level [2]. There are concerns that, absent specific policies for BTPs, a shared INN might permit a high proportion of ambiguously attributed safety reports.

SBPs were originally licensed in Europe in 2006, and since that time WHO, the biotherapeutic industry and drug regulatory agencies have considered various policy alternatives for naming of BTPs. These policy options include use of unique trade names, use of the WHO INN Greek letter policy, special INN naming rules for SBPs, development of various national nomenclature policies, and a proposal for a universally available biological qualifier issued by WHO.

5.2.1. Trade names

Reflecting that BTPs are often marketed with unique trade names, Europe has formally adopted a policy that SBPs should have the same INN as the RBP, but that

Table 2
Trade name attribution of biotherapeutic-related adverse event reports in pharmacovigilance systems

Product class	Region and timeframe	Trade name attribution (%)	Reference
Insulin	US 2005 to 2013	84%	Stergiopoulos et al., 2015
Somatropin	US 2005 to 2013	92%	Stergiopoulos et al., 2015
	Europe 2004 to 2010	91%	Vermeer et al, 2013
Filgrastim	Europe 2004 to 2010	85%	Vermeer et al., 2013
	Australia 2011 to 2014	58%	Amgen Inc., 2015
Erythropoietin	Europe 2004 to 2010	99%	Vermeer et al., 2013
Monoclonal antibodies	Netherlands 2009–2014	67%	Klein et al., 2016

each BTP should have a unique trade name [15]. This policy is supported by EC pharmacovigilance legislation requiring member states to take measures to ensure that prescriptions, patient records, and adverse event reports should refer to BTPs using the trade name [16].

Use of biotherapeutic trade names in adverse event reports is not universal and can vary according to the product class and region. Published data covering US, Europe and Australia show that use of trade names in adverse event reports varies from 58% for filgrastim products in Australia [17], 67% for monoclonal antibody therapeutics in the Netherlands [18], 84% for human insulin in the US [19], and greater than 90% for somatropin and epoetin products in Europe (see Table 2) [20].

While ambiguous product traceability in a portion of adverse event reports has not been associated with signal detection failures in the aforementioned countries it has been a serious issue in Thailand. Thai authorities were unable to identify the suspect product causing a cluster of pure red cell aplasia (PRCA), a serious adverse event, in patients receiving versions of epoetin alfa. At the time of the PRCA cluster more than a dozen originator and copy versions of epoetin alfa were marketed in Thailand, and medical records did not differentiate use of these products according to trade name [21].

5.2.2. INN Greek letter suffix

Sponsors for two SBPs of epoetin alfa followed WHO INN guidelines for glycosylated products and applied for new INNs with a distinct Greek letter suffix: epoetin kappa (SBP authorized in Japan) [22] and epoetin zeta (SBP authorized in Europe) [23]. The WHO summarized this application of existing INN policy to SBPs following an INN Program Open Session in 2012 [24]. However, this practice is voluntary and uniform application of the Greek letter policy would rely on drug regulatory agencies to enforce WHO INN policies rather than permitting pro-forma use of the reference product INN.

5.2.3. National non-proprietary naming policies

Pending a final nomenclature policy from WHO several regulatory agencies proposed or implemented unique national naming systems covering SBPs. The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) implemented a sequential

suffix approach wherein each subsequent SBP to a given RBP has a non-proprietary name comprising the INN followed by the designator "biosimilar" and a serial number indicating order of authorization, e.g., "Epoetin Alfa Biosimilar 1" [25,26]. In 2013 the Therapeutic Goods Administration (TGA) in Australia proposed using a compound suffix comprising the letters "sim" followed by a 3 letter qualifier unique to each SBP, e.g., "infliximab simfam" [27]. The TGA proposal was suspended in 2015 pending discussion of the WHO Biological Qualifier program [28].

The US Food and Drug Administration (FDA) also evaluated several approaches to differentiated naming, not necessarily limited to SBPs. In 2013 FDA authorized a non-biosimilar version of filgrastim using a 3-letter prefix in the non-proprietary name "tbo-filgrastim" [29]. Subsequently, FDA has proposed via draft guidance a system using a 4 letter suffix to be applied to all BTPs [30]. The first two FDA-licensed SBPs have proper names "filgrastim-sndz" [31] and "infliximab-dyyb" [32], and in 2015 FDA indicated via a proposed rule [33] that it intended to retrospectively modify the names of RBPs expected to be subject to biosimilar competition.

5.2.4. Biological qualifier

Taking into account the various options considered during consultations, as well as the emerging proliferation of national naming schemes, WHO proposed in 2015 to create a globally available biological qualifier (BQ) [34]. The BQ is proposed as a 4 letter code of random consonants, with a potential option of including a 2 digit "check sum" that could be used to verify the code integrity. The BQ would be an additional and independent identifier used in conjunction with the INN to facilitate product identification in prescriptions, patient records, and pharmacovigilance reports. The BQ would be administered by the WHO INN Programme on a voluntary basis and codes could be assigned to any biological substance having or eligible to have an INN. Unique codes could be assigned to each version of a biological substance that is manufactured by a corporate body using a single process and under the oversight of a global quality system.

As of mid-2016 the BQ program had not been implemented, and WHO was considering options for a pilot implementation program involving several member states [35].

5.2.5. Summary of naming policies

The introduction of SBPs has stimulated policy debates about the appropriate approach to ensure that products are properly identified in prescriptions, patient records, and adverse event reports. WHO and drug regulatory agencies agree that use of the INN is not appropriate for identifying BTPs, but there is disagreement about measures to ensure differentiation. Use of trade names is generally encouraged, but some jurisdictions may prefer to supplement this approach with a system of distinguishable non-proprietary names or qualifiers. The WHO Biological Qualifier program may offer a universal approach to assigning such qualifiers.

6. Interchangeability and substitution

The term "interchangeability" has a variety of meanings, depending on the policy framework that applies in a given jurisdiction. In one sense, the term conveys that a product may be expected to have a similar benefit-risk profile to another product in the same therapeutic class when used to treat a given medical condition. Such products may be therapeutically substituted with the involvement of a prescriber. In another sense, the term is used to indicate that a product is therapeutically indistinguishable at the patient level and hence may be substituted without the knowledge or intervention of a prescriber. Clearly, these two concepts cannot be captured in a single policy framework and it is important to differentiate them when covering the topic of interchangeability.

6.1. Interchangeability with respect to formulary and procurement policies

In the context of procurement and formulary practices, "interchangeability" often refers to the concept that two or more products are considered to be therapeutic alternatives in a given indication. Typically, such product classes would have the same mechanisms of action and would provide a comparable risk-profile at the population level. This concept may apply to any member of a therapeutic class (e.g., statins, anti-TNFs) and would, by definition, include SBPs and their RBPs, given that SBPs must have the same mechanisms of action and similar safety and efficacy in their approved indications. Indeed, a consensus report prepared by the European Commission defines interchangeability for SBPs to be "The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber" [36]. Here, we refer to this version of interchangeability as "medically-guided interchangeability".

According to the aforementioned definition, several European drug regulatory agencies have communicated that "interchangeability" is implicit in the approval as a biosimilar, meaning that patients may be initiated on or switched to the SBP with the involvement of the prescribing clinician, but not via pharmacy substitution [37]. In practical terms, drug procurement and formulary practices that would leverage medically-guided interchangeability to encourage use of SBPs are beyond the jurisdiction of drug regulatory authorities.

6.2. Interchangeability with respect to enabling pharmacy substitution

In a more stringent sense, interchangeability is understood to apply to a framework permitting substitution at the pharmacy level. For example, generics are considered therapeutically equivalent to their respective original brand medicines such that they may be safely substituted for the brand without the prior approval of the prescribing

clinician. Here, we refer to this version of interchangeability as "pharmacy-mediated interchangeability" [38].

There is currently no consensus regarding whether approval as a SBP is sufficient to permit pharmacy substitution, or whether additional evidence and risk assessment may be necessary on a product-specific basis. Accordingly, WHO SBP guidance states that such (pharmacy-mediated) interchangeability is beyond the scope of its scientific guidance and should be determined by competent authorities in member states [2]. Similarly, EMA guidance states that interchangeability should be determined at the European Union member state level [1]. Health Canada has indicated that approval as a Subsequent Entry Biologic (SEB) does not merit claims of bioequivalence or clinical equivalence [3]. Furthermore, given that biotherapeutic quality profiles can evolve over time, interchangeability assessments may not be durable and Health Canada therefore does not support pharmacy substitution [39]. The US FDA has stated that it is concerned about "inadvertent substitution" of non-interchangeable SBPs, reflecting its view that biosimilarity by itself is not sufficient to justify pharmacy-mediated interchangeability [30].

Notwithstanding the aforementioned disclaimers from WHO, EMA, Health Canada, and the US FDA several competent authorities are implementing pharmacy-mediated interchangeability frameworks that would permit pharmacy substitution of designated SBPs. For example, the enabling legislation for the biosimilars pathway in the US includes a provision for a regulatory determination of interchangeability in addition to the biosimilar pathway [4]. In 2015 the Australian Pharmaceutical Benefits Advisory Committee (PBAC) issued a policy memorandum stating that it could designate SBPs as suitable for pharmacy substitution, a policy measure known in Australia as "a-flagging" [40]. In both examples the competent authority (the US FDA or the PBAC, respectively) may assess additional evidence on a case-by-case basis to determine whether a given SBP is suitable for pharmacy-mediated interchangeability.

6.3. IFPMA position

In May 2016 the International Federation of Pharmaceutical Manufacturing Associations (IFPMA) published a position paper recommending elements of a sound policy framework for pharmacy-mediated interchangeability [38].

1) The specific SBP has received a formal interchangeability designation, contingent upon a competent authority performing a risk assessment establishing that the SBP is interchangeable with its RBP. The basis of the interchangeability assessment should be transparent to payers, patients and health care providers;
2) The SBP meets the regulatory requirements to be able to be approved for all indications of the RBP such that exclusions should thus only exist only for administrative or legal reasons (for example, intellectual property);

3) For BTPs that typically are administered multiple times in the course of treatment, the interchangeability designation should be justified including clinically relevant evidence that switching or alternating between the SBP and RBP would not impact safety or efficacy;
4) Legal frameworks have been established to permit the substitution of designated interchangeable SBPs while allowing the prescribing physician the 'right-to-refuse'; and
5) The jurisdiction has established a robust pharmacovigilance system, including adequate reporting of adverse events. Furthermore, the patient, pharmacist and the prescribing physician can readily access (for example via patient health records) unique identifiers for the dispensed BTP, including a unique product identification and batch information, so as to support pharmacovigilance.

6.4. Summary of interchangeability policies

There has been significant debate and divergence among stakeholders regarding the appropriate role of prescribers and pharmacists in determining which version of a BTP should be administered to a patient. During the initial period after SBP entry in Europe some policymakers cautioned that SBPs should be used to initiate treatment naïve patients, but not necessarily to switch patients who were already stable on an originator brand. In 2015, several drug regulatory agencies clarified their positions to encourage medically-guided switching. In reality, such practices were occurring all-along in some jurisdictions or markets that employed tender-based, single-source procurement policies.

Policymakers distinguish between such medically-guided interchangeability and policies that would permit substitution at the pharmacy level. Laws and policies in the US and Australia now permit substitution of designated SBPs following a case-by-case evaluation by a competent authority. Elements of these interchangeability evaluation frameworks may include assessments of whether the SBP may have a disproportionate risk in certain populations and of data supporting switching between the originator and SBP.

The IFPMA recommends that interchangeability frameworks should include case-by-case assessments by a competent authority. Furthermore, the IFPMA supports pharmacy practice policies that preserve a prescriber's option to preempt a substitution. To support a robust pharmacovigilance system, IFPMA believes that patient records should include accurate and complete information about the specific product dispensed and, furthermore, that these records are readily accessible to the prescriber and patient as well as the pharmacist.

7. The issue of non-comparable biotherapeutics products (NCBs)

As science-based pathways specific to the development, registration and surveillance of SBPs come into existence, some NRAs are still in the process of adapting their regulatory frameworks for BTPs. As a result, there are some countries

Table 3
Global situation for existing regulatory pathways

Countries where similar biotherapeutic product (SBP) guidelines have been adopted		Countries where SBP guidelines have not been adopted
Non-comparable biotherapeutic products (NCBs) that were approved before the implementation of country-specific SBP guidelines, and the product is currently in the market as approved by NRAs according to prior local regulations (e.g., generic or abbreviated pathway).	**NCBs that are approved after** the implementation of country-specific SBP guidelines based on an alternate or abbreviated pathway that has been adopted by the NRA.	**NCBs are approved as stand-alone products** and the data meet neither the WHO SBP Guidelines nor the standard for newly developed innovative BTPs. Clinical equivalence trials are not performed.

where intended copy biotechnological products have been licensed under regulatory pathways that are not appropriate for BTPs, such as (a) those that were intended for generic, chemically-synthesized pharmaceuticals, (b) abbreviated pathways requiring very minimal data, or (c) pathways where standards for approval are not well-defined (see Table 3). In these instances, the lack of specific guidance based on science-based assessment that is in line with the WHO Guidelines [2,41] on the Evaluation of Similar Biotherapeutic Products (2009) means that BTPs not shown to be comparable to a suitable RBP have been approved in certain markets. These NCBs belong to such classes as: interferons, erythropoiesis stimulating agents (ESAs), colony stimulating growth factors (CSFs) and somatropins. Monoclonal antibodies and fusion protein products have also been approved by these abbreviated pathways non-compliant with WHO guidelines.

NCBs are medicinal products that are developed without a complete comparability exercise even though a full regulatory data package of quality, safety and efficacy studies is sometimes provided. In contrast to SBPs, NCBs have not been shown to be similar in all three of these fundamental areas to a licensed RBP as defined by WHO guidelines. It is this totality of evidence that enables a SBP to establish a relationship to data originally generated for the originator RBP. In some cases, however, the sponsor of a NCB utilizes the safety and efficacy profile of another product rather than generating independent, substantive clinical evidence. Table 4 shows the differences with respect to quality, safety and efficacy data requirements between an RBP, an SBP meeting WHO expectations and associated guidelines, and a NCB at the time of market authorization application.

Since there is neither substantive stand-alone data nor sufficient evidence of similarity for a NCB, the basis of approval of such products is likely questionable. On the basis of this data gap, the balance of benefit versus risk is, in most cases, unknown resulting in substantial uncertainty. Consequently, there is little basis for reference to the safety and efficacy profile of another product and thus it is not surprising to see an increasing number of publications suggesting quality differences and lack of similarity between different NCBs and the RBP [42]. More recently safety signals

Table 4
Data requirements at time of marketing authorization

Data category	Reference Biotherapeutic Product (RBP)	Similar Biotherapeutic Product (SBP)	Non-comparable Biotherapeutic Product (NCB)
Quality	Full stand-alone quality data set.	Full stand-alone quality data set ***plus*** comprehensive side-by-side testing showing similarity to an originator RBP. Clinically meaningful differences not identified. Evidence of high degree of similarity is the basis for reduced non-clinical and clinical requirements for licensing.	Scope of quality data unknown. May not include any side-by-side assessment showing similarity to the originator RBP.
Safety	Full stand-alone non-clinical and clinical safety data, including immunogenicity assessment.	Side-by-side non-clinical and clinical safety data, including immunogenicity assessment, supporting claim of biosimilarity. Data generated in a comparative fashion on both SBP and RBP.	Scope of safety data unknown. May not include any side-by-side assessment showing similarity to the originator RBP. May only include very limited (or no) immunogenicity data.
Efficacy	Full stand-alone data set from pivotal efficacy trials.	Targeted clinical program comprising of comparative pharmacokinetic, pharmacodynamic, and efficacy trials, statistically powered to establish non- inferiority or equivalence to the RBP, which is included in the trials.	May include no or only very limited clinical data. Studies may not be powered to establish non-inferiority or equivalence to the originator RBP. Originator RBP may not be included in the clinical trial(s).

have been associated with their use, such as the pure red blood cell aplasia (PRCA) cases detected in Thailand [21].

7.1. The regulatory assessment of approved BTPs as an opportunity to tackle the issue of NCBs

The issue of approved BTPs not complying with WHO regulatory standards discussed above, and that many countries are impacted, is recognized by WHO. In their recently published guidance on "Regulatory assessment of approved rDNA-derived biotherapeutics" WHO is encouraging NRAs to undertake a stepwise regulatory review of all BTPs already authorized in their specific market by [43]:

1) Identifying the products that have been licensed with data which do not meet current WHO regulatory expectations.
2) Assessing the identified products and gaps, based on the product-specific considerations in order to decide the appropriate action to remedy the situation and

the timelines for implementing this action involving a risk-benefit assessment of the situation.

The product manufacturers should submit to the NRA within a short period of time a plan of action including an analysis of available and missing data in accordance with WHO guidelines as well as a description of measures, which may include interim assessments and proposed timelines, needed to address the identified gaps. It is further recommended that NRAs should assess the incoming data (e.g., quality/manufacturing, nonclinical and clinical data as needed) in a stepwise approach in several separate packages at different times – and on the basis of the outcome should decide on appropriate regulatory action e.g., whether or not the product license can be maintained.

In order to decide if a particular licensed product should be allowed to remain on the market during the review process described above the WHO document is proposing a risk assessment performed by the NRA taking into account among other factors:

1) The number of products on the market which have been licensed without adequate quality, nonclinical and/or clinical data.
2) The availability of alternative therapeutics on that market licensed locally with an adequate data package and/or also by an experienced NRA, meeting the standards of the relevant WHO guidelines.
3) The extent of the use of a BTP as well as availability of alternative products.
4) The seriousness of a potential lack of efficacy.
5) The ability of the pharmacovigilance system in the country should be considered to monitor and determine adverse reactions and/or efficacy problems.

Following through systematically with this concept will enable NRAs to properly mitigate the risk associated with NCBs but not leaving patients without treatment at the same time.

7.2. Capacity building and transparency as the key challenges for regulatory agencies in the upcoming years

Considering all the above, agencies specifically those in low and middle income countries may have difficulties – from a capacity and capability perspective – to follow up properly with all regulatory demands associated with BTPs and SBPs. In respective guidance documents [43] it is suggested that WHO and agencies experienced in the regulatory evaluation of BTPs should mentor less experienced agencies. Inter-agency trainings including the shared review of submissions may be considered. Also the exchange of assessment reports under confidentiality arrangements may be considered an option.

The mid or long term goal would be that currently affected agencies will be able to help each other and eventually move into a work-sharing mode analogous to those implemented in the EU. One of the key components to make this happen is regulatory convergence. Another recommendation [43] is the sharing of information

between NRAs regarding the basis for regulatory decisions on BTPs and SBPs e.g., via publicly available evaluation reports. This will build confidence in each other's capabilities and as a consequence the trust to potentially rely on each other's decisions.

The summary basis of decision documents of Health Canada, the EMA or the US FDA are examples of highly elaborated informative documents. Other agencies like MFDS from South Korea in 2014 or ANVISA from Brazil in 2015 also started the publication of summary assessment reports advancing an initiative from IPRF (International Pharmaceutical Regulators Forum) to propose a template for a "Public Assessment Summary Information for Biosimilars" (PASIB) that should help regulatory agencies to produce a standardized English language summary of their assessments of SBPs. In their implementation guidelines the IPRF is proposing a document based on WHO terminology that should be composed of three sections [44,45]:

1) Administrative information: Mainly completed by the applicant, this would contain details of the SBP and the RBP, the indications applied for, compliance with legal requirements, and links to additional information published by the NRA.
2) Data submitted and reviewer summary: The dossier and data content part would be filled in by the sponsor, and the review details by the authority. The quality part section would include the identification of analytical methods "at a high level, respecting confidentiality issues".
3) Reviewer conclusions: This section would contain concise high level conclusions to convey the basic information, such as whether the biosimilarity exercise was considered acceptable. It can mention areas where issues were raised during the review, and indicate whether all the claims proposed by the sponsor have been accepted (extrapolation of indications, for example). "Sufficient reasoning should be included in the PASIB to convey the outcome to a knowledgeable reader".

IPRF is encouraging NRAs who do not currently publish their reviews to engage in this initiative. Communicating details of what information was reviewed and how it was incorporated into decision-making may be also important for prescribers, patients and other stakeholders and can help them gain confidence in BTPs [43].

8. Conclusions

BTPs contain structurally complex active substances produced by living organisms. Due to their complexity and method of manufacture BTPs require distinct regulatory approval standards relative to chemically synthesized medicines. These considerations apply to originator medicines as well as to intended copy versions. The WHO and many NRAs have established guidelines or regulations concerning the

comprehensive similarity exercise needed for the development of SBPs. Implementation of these frameworks can be challenging, and must also consider mechanisms to normalize the regulatory status of historically licensed NCBs.

Policy makers are assessing measures to facilitate product-specific pharmacovigilance of BTPs. Policy makers and stakeholders are also considering the appropriate terms of use for SBPs, including whether patients may be switched to SBPs with the involvement of the prescriber or via pharmacy substitution.

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