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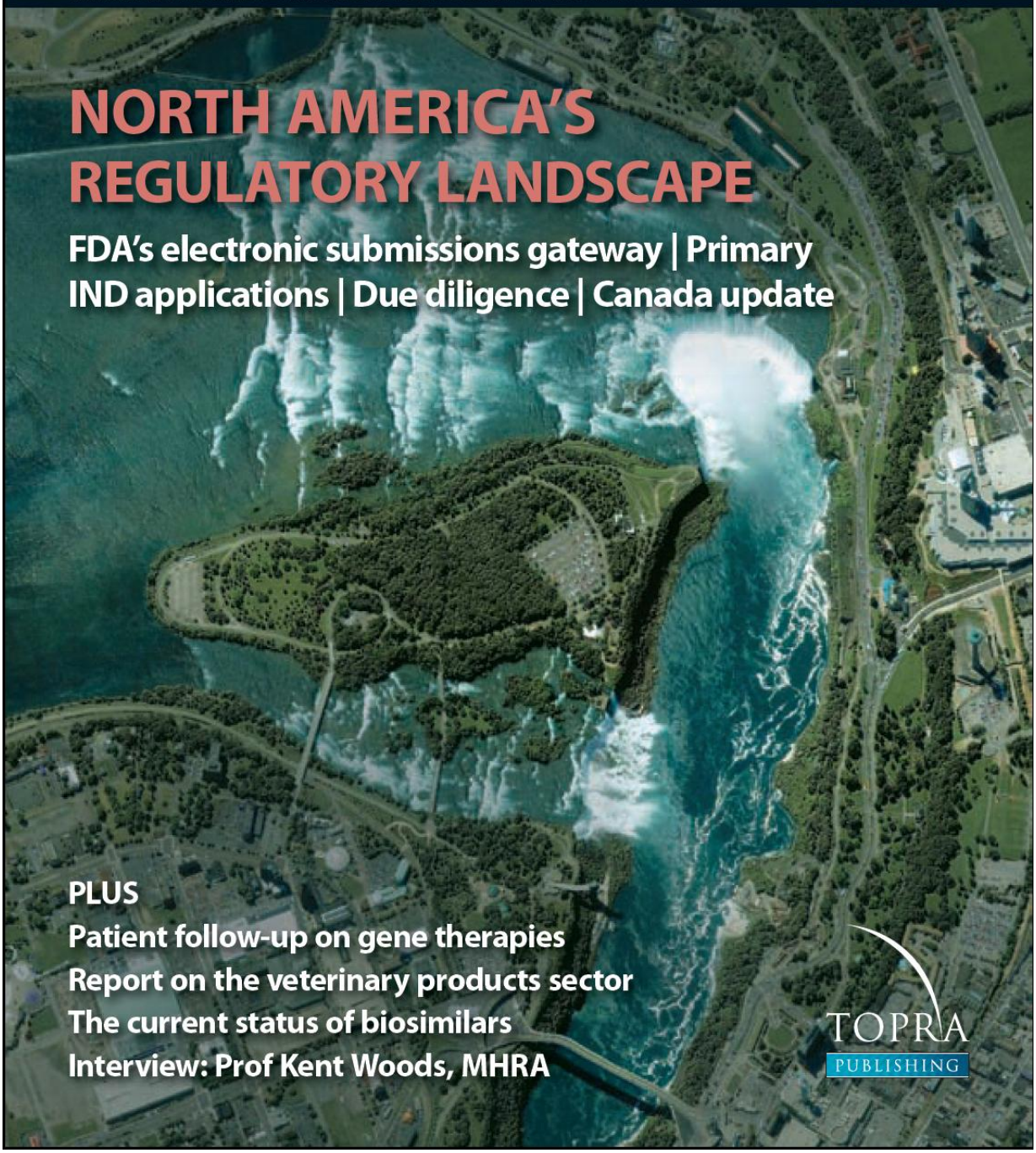

NORTH AMERICA'S REGULATORY LANDSCAPE

FDA's electronic submissions gateway | Primary IND applications | Due diligence | Canada update

PLUS

Patient follow-up on gene therapies

Report on the veterinary products sector

The current status of biosimilars

Interview: Prof Kent Woods, MHRA

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Cover illustration: *Aerial view of Niagara Falls and the Niagara River, which forms the US-Canadian border from New York State to Ontario.*

Photo credit: *NASA's Earth Observatory*

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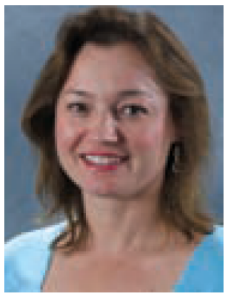
Regulatory updates –
Across the pond and around the globe



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Our September issue provides an update on various aspects of the evolving North American regulatory landscape. However, we still offer a global perspective that is essential for international regulatory professionals. Throughout the publication you will find practical advice and experience-based guidance that will help industry face the challenge of addressing regional regulatory requirements.

In our update on Canada, you will find news on subsequent-entry biologics (the Canadian term for biosimilars), medical isotopes and a briefing on FDA medical device audits by Canada, the EU, Australia and Japan. Since biosimilars are currently such a critical topic, we have included, "The current status of biosimilar biologics – Part 1: An international perspective", the first in a two-part series on the topic. This piece provides a detailed discussion of the recent changes to biosimilars regulations and guidances in key regions, and includes a discussion of the recently published guidance from the WHO.

As we expand our global perspective, you can read "A closer look at the MHRA", an abridged version of an in-depth interview conducted with Prof Kent Woods, Chief Executive of the UK regulatory agency. Prof Woods shares his insight from a leadership position and discusses current operational and strategic topics within the agency. If you would like to read the full interview, go to *www.topra.org/useful-articles*.

If you are interested in Advanced Therapy Medicinal Products (ATMPs), you will appreciate "Regulatory and scientific considerations for the follow-up of patients treated with gene therapy medicinal products: an EU perspective". This article offers a detailed analysis of the recent guidance issued by the gene therapy working party (GTWP) at the European Medicines Agency (EMA) which provides useful recommendations on the risk assessment of gene therapy treatment and on long-term follow-up programmes. If you are responsible for or are considering submitting an electronic application to the US Food and Drug Administration, you will find practical suggestions in "Getting Started with the FDA's Electronic Submissions Gateway". In this piece, the authors share their experiences in planning, implementing and using the ESG. If you happen to be responsible for an upcoming Investigational New Drug (IND) application, you will also want to read "Managing Primary IND Applications with the FDA", where the author shares important points to consider as you plan for this milestone regulatory process. And if you are evaluating a product (for licensing or acquisition), you will want to read "Delving into product development due diligence for US regulatory submissions". In this piece the author shifts focus from documents to data in the due diligence process and offers guidance to avoid common mistakes that often result in lost time, money and resources and misguided acquisitions.

> As the regulatory landscape continues to evolve at a rapid pace, it is important to maintain awareness, sustain current knowledge and share practical experiences

Finally, if you are involved in the development of a veterinary product, our report on a recent international conference in Paris updates you on the impact of VICH and its future expectations, with global outreach being a recurring theme throughout the agenda. As you can see by the diversity of topics and the number of regional changes that are occurring within the various agencies, the regulatory landscape is continuing to evolve at a rapid pace. It is important to maintain awareness, sustain current knowledge and share practical experiences as we continue on this ever-changing journey.

If you are located in North America, you may consider participating in TOPRA North America's educational events and programming. We have conducted seminars and networking events throughout the region and are continuing to cultivate our membership. The TOPRA North America team is always looking to improve our educational offerings and expand our reach so if you would like to meet with industry colleagues and share your experiences, we would welcome your participation. To learn more about TOPRA North America, visit our webpage: *http://www.topra.org/topra-north-america*.

The current status of biosimilar biologics – **Part 1: An international perspective**

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Keywords

Regulatory framework; European Commission; European Medicines Agency (EMA); US FDA; Japanese Ministry of Health, Labour and Welfare (MHLW)/Pharmaceuticals and Medical Devices Agency (PMDA); Health Canada; World Health Organisation (WHO)

Abstract

Europe set a precedent in 2006 by approving the first biosimilar medicines for human use. This led to the establishment of supporting laws and regulations in other major regions such as Canada in 2009, South Africa in 2009, Australia in 2009, Malaysia in 2009, the US in 2010 and a WHO international guidance in 2010. This article is the first in a two-part discussion of the evolution of global biosimilars guidance and regulations. Part 2, to be published in an upcoming issue of Regulatory Rapporteur, *will look at the global development landscape for biosimilars.*

Setting the global stage

Biosimilars, similar biotherapeutics, similar biological medicinal products, follow-on biologics and precedent biotechnology drugs are all terms used in different regions of the world to describe subsequent versions of innovator biopharmaceutical products. In the same way that the terminology differs, regulatory requirements also vary from region to region.

Europe: The legal framework for biosimilars in Europe was laid down by European Directives in 2003/63/EC and 2004/27/EC, opening the way for implementation by the European Commission and the European Medicines Agency (EMA). The EMA defines a biosimilar product as "similar to a biological medicine that has already been authorised (the 'biological reference medicine'), and contains the same active substance as the biological reference medicine. Biosimilar and biological reference medicines are used to treat the same disease at the same dose, and possess no significant differences in terms of safety or efficacy."[1]

On receipt of the marketing authorisation (MA) by the European Commission, therefore, the recommendation is that the current marketed product can be substituted by its biosimilar in the EU.

The US: As of July 2010, the US FDA had not issued a guideline on biosimilars but there is provision in the Patient Protection and Affordable Health Care (PPAHC) Act passed by the US Senate for approval of biosimilar biological products.[2] The interpretation of the law will unfold gradually into a regulatory framework, and FDA advice on biosimilar development plans should be sought at the FDA divisional level.[3]

Japan: Japan's Ministry of Health, Labour and Welfare (MHLW) published the draft 'Guidelines for the Quality, Safety and Efficacy Assurance of Follow-on Biologics' in September 2008 (step 1) and updated it on 4 March 2009 (step 2).[4] This development appears to reflect the new openness of the Japanese MHLW/Pharmaceuticals and Medical Devices Agency (PMDA) and its increasing acceptance of international data and innovation. The reference product is described as a "precedent biotechnology drug" and acceptability of "head on" data as pivotal or supporting data derived from a reference sourced in another region should be discussed with the PMDA.

Canada: On the granting of a Notice of Compliance to a Subsequent Entry Biologic (SEB), according to Health Canada, "the SEBs are not 'generic biologics' and many characteristics associated with the authorisation process and marketed use for generic pharmaceutical drugs do not apply. Authorisation of an SEB is not a declaration of pharmaceutical and/or therapeutic equivalence to the reference biologic drug".[5]

The WHO: The World Health Organisation (WHO) developed a guidance from 2008 with a vast international authorship which was finalised in 2009 and published recently in 2010. It is based largely on the European experience, but does draw on other sources, and is a thorough examination of the issues, and a proposal for a scientific basis of approval of "similar biotherapeutic products" (SBPs).[6]

First biosimilar approvals

The first biosimilar products approved in Europe and the rest of the Western world were somatropin (human growth hormone) products: Omnitrope,[7] whose market authorisation holder (MAH) is Sandoz, Austria; and Valtropin,[8] whose MAH is BioPartners, Germany (with Swiss headquarters). Both were authorised in the EU by the European Commission in April 2006.[7,8] The approvals were based on comprehensive pharmaceutical comparisons against two different reference medicinal products (RMPs): Genotropin for Omnitrope, and Humatrope for Valtropin, and had to be evaluated for additional criteria (for Valtropin these included: noninferiority,[9] equivalence,[10] sensitivity[11] and fermentation[12]). As a result, the two approved biosimilar products had different label claims for specific indications and pharmaceutical characteristics derived from their respective RMPs.

Legal concerns resulted in lengthy MAA submission validation times for the first biosimilars. Among the issues was the release to the rapporteur/co-rapporteur of regulatory information on the reference product held at a national level. For example, Humatrope was approved by the old Concertation Procedure nearly two decades ago, with the Netherlands as the reference member state. Therefore, with the submission of Valtropin, the original MAA data on Humatrope had to be released to the

EMA. As a result of the pioneering nature of these submissions and the unprecedented regulatory and legal issues, Valtropin's validation took around three months instead of the standard ten days.

Omnitrope was submitted twice before it achieved authorisation by the Commission, even though the European Committee for Proprietary Medicinal Products (now the Committee for Medicinal Products for Human Use, or CHMP) gave it a positive opinion following the first submission in 2004–05.[13] The Commission would not agree to a bibliographic submission, which the applicant had advocated based upon the marketed product's well-established use. This legal basis was not accepted, and the applicant had to generate additional clinical data for a second application, including an open-label comparative study.

Subsequent biosimilar approvals

Additional biosimilar products approved in the EU have been five approvals in 2007 for erythropoietin, developed by Sandoz and Stada, using Eprex/Erypo as the RMP, with parallel MAAs (from Sandoz, Hexal and Medice; and Stada and Hospira) using the same erythropoietin product under different names.[14] There were four approvals in 2008 for filgrastim granulocyte colony stimulating factor, developed by Ratiopharm and Teva, with Neupogen as the RMP – again with parallel submissions using the same granulocyte colony stimulating factor product.[15] There were two further filgrastim approvals in 2009 (Hexal and Sandoz).

Up until July 2010, there have been 17 MAA submissions leading to 13 approvals,one negative opinion (interferon alpha) and three withdrawals (insulins). Europe has clearly taken the worldwide lead in approving biosimilars, based on the legal framework established in 2004 and the regulatory precedents set in 2006.

European progress

For four years the EU Commission, through the vehicle of the CHMP/EMA, has authorised biosimilars from many classes of proteins, facilitated by many general and biologic product-specific guidances.[16] However, a special challenge is presented by the monoclonal antibodies (MAbs) which are hugely important as a class with more than 20 approved new products. The will of the EU regulators to open up this opportunity was evident from the reflection paper of the current chair of the Biosimilars Working Party (BWP).[17]

However, MAbs pose the problem of a much larger molecule (150KDa) and greater complexity including glycosylation and heterogeneity. This can make extrapolation from one indication, such as psoriasis, to another, such as rheumatoid arthritis, unacceptable. Further problems are that a typically CHMP/EMA-expected equivalence study can be much larger in patient numbers than the originator's standalone development; also pharmacokinetic equivalence studies require substantially large numbers and have to be of parallel design, due to the long half-life of MAbs, presenting new confounding factors. It is expected that there will soon be a new guidance on MAbs.[18]

In 2010 there is a new guidance on nonclinical and clinical recombinant follicle stimulation hormone (FSH) development.[19] This is the first time follitropin alpha and beta has been addressed, as there are serious safety concerns, namely, hypersensitivity, ovarian and congenital maltransformation risks for women with assisted reproductive technologies (ART) using this narrow therapeutic range protein.

Three products containing recombinant INF-β are currently centrally approved in the EU; they differ with respect to their E.coli or CHO fermentation molecular structure, injection route, recommended posology and multiple sclerosis (MS) indications; also, MS disease heterogeneity and INF-β multifaceted immunomodulatory mechanisms.[20]

Also new is a revised adopted EPO guideline coming into effect in October this year, despite several EPO approvals.[21] This illustrates the necessary caution in developing any biosimilar without seeking any prior and current CHMP/EMA Scientific Advice. The requirements can change, and there are invariably sponsor product-specific issues with such complex molecules.

International progress

The first international approvals for biosimilars occurred in 2006 and 2007, when G-CSF and the MAb rituximab were approved in India based on pharmaceutical, nonclinical and pharmacokinetic/pharmacodynamic (PK/PD) data. Biosimilars have also been approved elsewhere in recent years, including some South American countries and China. Canada, Australia, South Africa and Malaysia have largely adopted the European guidelines. However, a regulatory framework has not yet been established in the US, (even though the legal basis was introduced in Spring 2010), Korea and many other countries.

In Japan, one epoetin biosimilar (EPO JR013) was submitted to the Pharmaceuticals and Medical Devices Agency (PMDA) in 2008 by Japan Chemical Research and Kissei, using a virus-free, non-serum-based, fermentation.[22a] The first Japanese biosimilar approval made public in June 2009 was that of somatropin (Sandoz); presumably its supporting dossier was submitted well before the current guideline.[22b]

At the international level, the WHO began an initiative in 2008 to harmonise the definition of biosimilars, and, in particular, the data requirements of the RMP of biosimilars.[23] This process is now concluded in 2010 with the final WHO guideline.[6]

Health Canada considers that SEBs are not a new class of biologics.[5] They are considered as second versions of biologics that already exist on the Canadian market and whose patents have expired. No new regulations have been developed for SEBs, instead the criteria that the CHMP/EMA has used since 2006 have been adopted. There is Canadian draft guidance: 'Information and Submission Requirements for Subsequent Entry Biologics (SEBs)'. The first approval (Omnitrope) took two years.

US progress

Regarding the US, in December 2009 the US Senate passed the PPAHC Act (H.R. 3590), a comprehensive healthcare reform legislation. In March 2010, the US House of Representatives also passed this legislation; and it was signed into law by the President on 23 March 2010. These two statutory provisions together are referred to as the Biologics Price Competition and Innovation (BPCI) Act. Included is a provision (Section 7002) amending the Public Health Service Act (PHSA) to permit approval of biosimilar biological products through an abbreviated biological license application (ABLA) submitted to the FDA.[2]

The FDA's working group, the Biosimilar Implementation Committee (BIC), will ensure that the process of evaluation, review and approval of biosimilar products will be achieved in a consistent, efficient and scientifically sound manner across the FDA Divisions and Centers. This committee is co-chaired by Dr Janet Woodcock, director of the Center for Drug Research and Evaluation (CDER) and Dr Karen Midthun, acting director of the Center for Biologics Evaluation and Research (CBER). This cross-centre group also has members from the Office of Chief Counsel

and the Office of the Commissioner. Two review committees have also been chartered; the CDER Biosimilar Review Committee (chaired by Dr John Jenkins) and the CBER Biosimilar Review Committee (chaired by Dr Robert Yetter). Mixed membership from both centres will ensure uniformity in addressing product-specific reviews and issues relating to scientific methodology.

The goal of the BPCI Act is similar in concept to that of the Drug Price Competition and Patent Term Restoration Act of 1984 (also known as the Hatch-Waxman Act) which created abbreviated 505(j) pathways for the approval of drug products (as abbreviated new drug applications, or ANDAs) under the Federal Food, Drug, and Cosmetic Act (FD&C Act), and once approved they became Therapeutic Equivalents and appeared in the FDA's "Orange Book". That Act also permitted an abbreviated path for the approval of a "follow-on" protein under an NDA 505(b)(2) pathway for proteins such as somatropin, or hyaluronidase, but these could not be therapeutic equivalents nor "biosimilars".

The reference biologic products (RBPs) for future US biosimilars were approved under the PHS Act under the jurisdiction of CBER. Therefore, it is under the BPCI Act, and not the FD&C Act, that a sponsor may seek approval of a "biosimilar" product, specifically under a new section 351(k) of the PHS Act.

It is helpful to position the biosimilars in the light of US regulatory history from a legal standpoint.[24] That is, comparing an NDA versus a BLA as a standard for approval/licensing: an NDA is subject to the FD&C Act, hence the requirement for approval is the "substantial evidence" of effectiveness (in the form of "adequate and well-controlled studies"); and the product is "safe for use under the conditions prescribed".

As RBPs were approved under a BLA, which is subject to the PHSA, the requirement for BLA approval, and hence a biosimilar BLA, is that the product is "safe, pure, and potent", and the manufacturing facility meets "standards designed to assure" this.

This legal and regulatory background explains the statement in the FDA 2008 position document that: "A biological product may be demonstrated to be "biosimilar" if data show that the product is "highly similar" to the RBP notwithstanding minor differences in clinically inactive components and there are no clinically meaningful differences between the biological product and the RBP in terms of *safety, purity and potency*."[25]

If the biosimilar product is interchangeable it may be substituted for the RBP by a pharmacist without the intervention of the prescribing healthcare provider.[25]

Under the new BPCI Act, a biosimilar filing must respect the new 12 years' data exclusivity for the reference product, the innovator's biologic. That is, no biosimilar will be approved before expiration of a 12-year (plus six months for a US paediatric exclusivity) period from the date of first approval. Additionally, no biosimilar application will be accepted by the FDA during the first four years of data exclusivity from that date. The FDA will approve an interchangeable biosimilar application if: (1) it is found to be "biosimilar"; (2) it can be expected to produce the "same clinical result as the reference product in any given patient"; (3) it can be alternated or switched with use of the RBP without risk to the patient in terms of safety or diminished efficacy compared with use of the RBP alone.

Incentives are also provided for the first approved interchangeable biosimilar: a one-year exclusivity from first marketing date of first approved interchangeable biosimilar, or 18-42 months' exclusivity after approval, depending on legal action by the innovator.

BLAs have no mechanism for listing of relevant drug substance, drug product, and method-of-use patents in the FDA's Orange Book, unlike NDAs. Proposed legislation for biosimilar products would not create an Orange Book for biologics, which unfortunately complicates the procedure by a higher risk of litigation between parties prior to FDA approval of a biosimilar, therefore it is advisable to resolve patent disputes well before the BLA submission.

The FDA and EMA are currently collaborating closely in many fields,[3] and there are regular exchanges of information on the European biosimilars review experience. This background knowledge together with the FDA's extensive but focused product and therapeutic area insights at the divisional and centre levels should afford efficient FDA guidance at Type B meetings for sponsors on the development of biosimilars. Prior European experience of sponsors with biosimilars would likely greatly facilitate preparation for an FDA meeting.

Progress by the WHO

The final WHO guidance, on "similar biotherapeutic products" (SBPs), published just before this article went to press, incorporates the fundamental principles adopted by the European authorities based on many scientific advices, guidances, basis of approvals of products, but is also very well written and comprehensive.[6] There are, however, additional aspects which it covers uniquely and which should prove beneficial even to experienced European biosimilars experts.

The WHO will not address matters to be defined by the national authorities such as intellectual property issues, interchangeability and substitution of an SBP with a reference biotherapeutic product (RBP), and labelling and prescribing information.

The choice of an RBP is of critical importance for the evaluation of SBP and needs to be justified to the national regulatory authority and licensed based on full quality, safety and efficacy data. Therefore, a marketed SBP by another manufacturer cannot be an RBP.

The WHO recommends a general rule, that the product should be expressed and produced in the same host cell type as the RBP (eg, E.coli, CHO cells, etc.) in order to minimise the potential for important changes to critical quality attributes of the protein and to avoid introduction of certain types of process-related impurities (eg, host cell proteins, endotoxins, yeast mannans) that could impact clinical outcomes and immunogenicity. The WHO allows exceptions. For example, somatropin produced in yeast[12] cells appears to have similar characteristics to somatropin expressed in E.coli.

Also,specifically raised by the WHO is that head-to-head accelerated stability studies comprise an important element of the determination of similarity between an SBP and an RBP to unmask "otherwise-hidden properties".

The prerequisites for additional nonclinical studies as part of the overall comparability exercise is the same as for Europe, and includes significant differences in the cell expression system compared with the RBP in purification methods used, the presence of a complex mixture of less well characterised product- and/or process-related impurities. Other cases are when mechanism(s) of drug action are unknown or poorly understood, the drug substance is toxic and/or has a narrow therapeutic index, or there is limited clinical experience with the RBP.

Antibody measurements should be included in the repeat dose toxicity study to interpret the toxicokinetic data.

Interestingly, the WHO is flexible with regard to the PK study on the 90% confidence intervals of the ratio of the population geometric means (test/ reference) for the rate (C_{max}) and extent of absorption

($AUC_{0-\infty}$) falling outside the traditional 80-125% equivalence range; that is, the SBP may still be considered similar to the RBP provided there is sufficient evidence for similarity from the quality, nonclinical, PD, efficacy and safety comparisons.

The study population and dosage should represent a test system that is known to be sensitive to detect potential differences between the SBP and the RBP, just as with the European requirements. The WHO illustrates this biosimilar product development principle of "sensitivity" by describing PK/PD or clinical study requirements of insulins, GCSFs and growth hormones.

The WHO also discusses clinical and statistical considerations very specifically. In principle, 'equivalence' designs (requiring lower and upper comparability margins) are clearly preferred for the comparison of efficacy and safety of the SBP with the RBP. Non-inferiority designs (requiring only one margin) need to be justified. 'Similar' efficacy implies that similar treatment effects can be achieved when using the same dosage(s); hence, in the head-to-head comparative trial(s), the same dosage(s) should be used for both the SBP and RBP. In cases for which the medicinal product is titrated according to treatment response (eg, epoetin, insulin) rather than given at a fixed dosage (eg, somatropin in GH-deficient children), equivalence/non-inferiority should be demonstrated not only with regard to treatment response but also with regard to dosage. This is best achieved by defining co-primary endpoints that also include dosage.

Generally, equivalence trials are preferable to ensure that the SBP is not clinically less or more effective than the RBP when used at the same dosage(s), and to justify extrapolation to other indications. For medicinal products with a wide safety margin, non-inferiority trials may also be acceptable, according to the WHO. However, non-inferior efficacy, by definition, does not exclude the possibility of superior efficacy of the SBP compared to the RBP which, if clinically relevant, would contradict the principle of similarity. The WHO provides extensive statistical advice on every scenario.

Conclusion

In spite of major obstacles there has been genuine progress in our understanding of the new paradigm of the development, registration, use and acceptance by the payor, patient and physician of biosimilar medicines internationally. Furthermore, evolving guidances and regulations on an international level are spurring new discussions of strategy and increased communication between agencies and sponsors of biosimilars. As regulatory frameworks continue to evolve, the substantial regulatory burden, complex logistic challenges and costs of biosimilars development will emerge.

Part 2 of this series will focus on the important sponsor considerations throughout the biosimilar development process.

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