

# Norms and standards

## Biotherapeutics and biosimilars

**Advances in biotechnology have enabled scientists to produce biological medicinal products that provide new treatment options for a wide range of diseases, including life-threatening ones. However, these complex medicines are expensive to develop and produce, and their high cost potentially affects equitable access to them.**

**Biosimilars – products that are very similar to already approved biotherapeutic products – could make this new generation of medicines available more widely at a more affordable cost to health systems. This article describes some recent developments in global efforts to create regulatory pathways and naming systems for biotherapeutics, including biosimilars.**

### Biotherapeutic products

New technologies have made it possible to produce large quantities of medicines that are derived from living systems.

Biotherapeutic medicines can now be produced in large quantities in bacteria, yeast, transformed cell lines of mammalian origin (including human origin), insect and plant cells, as well as transgenic animals and plants. In most cases this is done by using genetically modified cells, which are engineered to produce the desired proteins.

Some biotherapeutics are proteins that are naturally present in the human body, such as growth hormones, insulin, erythropoietins, enzymes or antibodies. Others are biologically active proteins that do not exist in nature and are produced by techniques such as recombinant deoxyribonucleic acid (rDNA) technology. Examples include chimeric, humanized or fully human monoclonal antibodies, antibody-related proteins or fusion proteins. These substances can treat a wide range of diseases, including various forms of cancer, heart attacks, stroke,

diabetes, rheumatoid arthritis, multiple sclerosis, hepatitis C, chronic renal failure, anaemia, low white blood cell counts, inflammatory bowel disease and others.

Biotherapeutics are more complex than chemical medicines and are therefore more challenging and more expensive to develop and produce. Often they are initially approved for an indication while they are being studied further, and the licence is subsequently modified to approve additional uses as new clinical data become available. Biotherapeutics also present special safety challenges because they are immunogenic, meaning that they are recognized as foreign proteins in the body and can trigger unwanted immune reactions.

### *Medicines of the future*

Recognizing that biotherapeutics provide new treatment options to save lives and restore health, the 67<sup>th</sup> World Health Assembly adopted a resolution on access to biotherapeutics (1), calling for effective regulation and equitable access. This is a timely call, considering the speed at

which the markets for new generation of medicines are evolving. According to a recent report (2) biologic medicines accounted for 27% of pharmaceutical sales in Europe at the end of 2013, with a year-on-year growth almost three times that of the pharmaceutical sales value as a whole, and with patents for many top-selling biologicals expiring or due to expire by 2020.

### **Biosimilars**

The expiry of patents and/or data protection for the first major group of originator's biotherapeutics has ushered in an era of products that are designed to be "similar" to a licensed originator product. These products rely for their licensing partly on existing information regarding safety and efficacy obtained with the originator products. Biosimilars – also called "similar biotherapeutic products", "follow-on biological products" or "subsequent entry biologics" in different regulatory systems – can bring down the cost of medicines by increasing competition and can thus increase patient access. A similar development was seen in recent decades with generic versions of chemical medicines.

#### *Biosimilars are not generics*

Although the market aspects appear similar, there are important differences between generics and biosimilars. While generics are exact copies of the chemical structures of their reference products, biosimilars are highly complex molecules produced in living systems with inherent variability. By definition they will not be identical to their biotherapeutic reference products. This has implications for regulatory assessment.

For generics, regulatory safety and efficacy assessment relies on a relatively

simple premise: If a generic is shown to be bioequivalent (distributed in the body at the same rate as the reference product) then it can be assumed to be equally safe and effective as the reference product, and it will be interchangeable with the latter, meaning that it can be substituted or switched without consulting the prescriber.

For biosimilars – which are not identical to the biotherapeutic reference product – the 'generic' approach by demonstration of bioequivalence is not sufficient to ensure adequate development, regulatory assessment and licensing. More sophisticated scientific approaches are required to compare a biosimilar with its reference product based on both non-clinical and clinical data. Tailor-made studies are needed for each biosimilar to define the degree of difference from its reference product, and to determine whether it is interchangeable with the reference product and whether its efficacy, safety, immunogenicity and interchangeability can be assumed ("extrapolated") for a different indication or in a different population than that studied.

### **Regulation of biosimilars**

#### *WHO guidance*

WHO provided guidance on biosimilars in 2009 (3). The guidance text is a "living document" to be developed further in line with advances in scientific knowledge and experience.

WHA Resolution 67.21 calls for an update of the WHO guidance text, taking into account the technological advances for the characterization of biotherapeutics and considering national regulatory needs and capacities. The 2014 International Conference of Drug Regulatory Authorities (ICDRA) adopted a number of recommendations on biotherapeutics

and biosimilars (4), identifying some areas to develop further in the WHO guidance. These include: extrapolation of indication, special considerations for evaluation of monoclonal antibodies, acceptance criteria and evaluation of reference biotherapeutic products including the reliance on reference agencies, and the design, conduct and interpretation of studies to evaluate comparability.

At its 65<sup>th</sup> meeting the WHO Expert Committee on Biological Standardization decided to initiate an update of the WHO biosimilars guidance and to implement recommendations from the 16<sup>th</sup> ICDRA meeting on biotherapeutics including biosimilars (5).

### *National requirements*

While WHO provides norms and standards, national regulatory oversight is what ensures the quality, safety and efficacy of biotherapeutic products. Countries need efficient pathways to approve clinical trials and biotherapeutic products. Once products are on the market, effective pharmacovigilance systems are needed to track adverse events, including unwanted immune reactions.

National regulations on biosimilars have evolved in the last decade. The European Medicines Agency (EMA) published its first regulations for biosimilars in 2005, and on 1<sup>st</sup> June 2015 there were 19 biosimilars listed on the EMA website<sup>1</sup>. Biosimilars regulations based on EMA and/or WHO guidelines have been introduced in a number of countries, with some adaptations to suit the national context, for example to lower the barriers of clinical trial requirements or to accept reference products that are not licenced domestically.

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<sup>1</sup> [www.ema.europa.eu](http://www.ema.europa.eu) – Find medicine – Human Medicine – (browse by type): [Biosimilars](#)

In the United States a pathway for approval of biosimilars was put into place after the signing of the Biologics Price Competition and Innovation Act on 23 March 2010 by President Barack Obama. The FDA's biosimilars regulation guideline came into force in 2014, and in March 2015 the first biosimilar was approved under the new guidance (6). In September 2014 the FDA published the first edition of its “Purple Book”, a set of lists of licensed biological products.

Going forward, WHO guidelines will provide a valuable reference for establishing new national regulatory requirements or updating existing ones, and for promoting convergence at the global level to enable regulatory cooperation.

### *Naming of biosimilars*

Naming of biotherapeutics and biosimilars has important implications for a range of stakeholders including regulators, the pharmaceutical industry, health systems, health professionals and patients.

Different naming systems for biosimilars are currently in use in countries. Some regulatory authorities have been using the International Nonproprietary Name (INN), while others have added a qualifier which in some cases incorporates the company name. To complicate matters further, a product may be viewed as a biosimilar to a given reference product in some jurisdictions but not others.

Various arguments have been voiced for and against giving distinct names to biosimilars. Those in favour argue that each biosimilar differs from its reference product and from other biosimilars, and that distinct names will make it easier to know which product a patient is receiving, to ensure correct use and to track adverse events. Those against reason that by

definition biosimilars are highly similar to the reference product with no clinically meaningful differences, and that a common name is therefore sufficient and will help to limit marketing costs, making products more affordable for health systems.

Following requests from several drug regulatory authorities the WHO INN Programme has proposed a Biological Qualifier scheme (7), which is currently under discussion. Recognizing the value of regulatory convergence as a tool to increase global access to safe, effective, quality biosimilars, participants to the 16<sup>th</sup> ICDRA recommended that a clear terminology should be defined for naming these products, enabling a clear identification of the evaluation pathway (4).

Systems in countries are meanwhile evolving. A placeholder non-proprietary name was assigned to the first biosimilar approved in the United States through the new abbreviated regulatory pathway for biosimilars (6), and in Australia an interim system for naming of biosimilars has been proposed given that the WHO proposal has superseded the previous position on which the national naming policy was based (8).

## Conclusion

Ensuring regulation of biotherapeutic products in WHO Member States along globally consistent principles is an urgent matter with significant public health impact. Information and education of all stakeholders will also be crucial, as doctors' and patients' perceptions of biosimilar medicines, local pricing and reimbursement regulations and procurement policies and terms will all influence equitable access to biotherapeutics.

Implementation of WHO standards for biologicals is recognized as having a great

value from a stakeholders' perspective. WHO envisages a comprehensive review of the current concept of biological standards and their use, starting with standards for biotherapeutic products, including biosimilars, in 2015. However, the scope of work and required resources to cover the continuously growing expectations exceed the current capacity of the Organization's Secretariat. Discussions will continue at WHO to plan this work and to identify a new funding strategy.

## References

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- 3 [Guidelines on evaluation of similar biotherapeutic products \(SBPs\).](#) In: WHO Expert Committee on Biological Standardization. Sixtieth report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 977),
- 4 [16th International Conference of Drug Regulatory Authorities \(ICDRA\).](#) WHO Drug Information. 2014; 28(3): 297-306.
- 5 WHO Expert Committee on Biological Standardization. [Main outcomes of the meeting held from 13–17 October 2014.](#)
- 6 U.S. Food and Drug Administration. [FDA approves first biosimilar product Zarxio.](#) [News release]. 6 March 2015. (See also page 157.)
- 7 WHO Programme on International Nonproprietary Names (INN). [Biological Qualifier. An INN Proposal.](#) INN Working Doc. 14.342. Revised draft July 2014.
- 8 Therapeutic Goods Administration. [Evaluation of biosimilars.](#) [Web page]. 20 April 2015. (See also page 153.)