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COMMENTARY

The road to biosimilars in rare diseases - ongoing lessons from Gaucher disease

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A 'biosimilar' is a biotherapeutic product that has provensimilarity in terms of quality, safety and efficacy to a licensed reference product (RP) (Table 1). The term 'biosimilar' was introduced for biologics because their complexity makes it impossible to make an identical copy. In contrast, a 'generic' is an exact copy of a small-molecule drug with a known chemical structure and a fixed number of atoms. With patent expiries of biologics, biosimilars have been proclaimed as a means to broaden access to treatment and reduce costs.

In addition to guidelines published by the World Health Organization (WHO) in 2009,[1] biosimilar development is strictly regulated by the US Food and Drug Administration (FDA),[2] and the European Medicines Agency (EMA)[3] (Table 1). These organizations require that similarity to a RP should be demonstrated by performing comprehensive comparability studies that confirm pharmaceutical quality, biological activity, safety (including immunogenicity) and efficacy. Development of biosimilar guidelines in regions with high regulatory vigilance, such as the European Union (EU), the USA, and more recently in Japan, Canada and Australia, has contributed to increased usage of biosimilars among healthcare professionals (HCPs). However, guideline adoption in regions such as Latin America, Asia and non-EU countries remains slow, and a historical lack of regulatory scrutiny in these areas has led to the controversial approval of so-called "Non-Comparable BioTherapeutics" (NCBTs) that do not comply with established standards for biosimilar approval. In this article, we

TABLE 1 Key differences between WHO, FDA and EMA biosimilar guidelines

	WHO[1]	FDA[2]	EMA[3]
Definition	A biosimilar should be compared to an RP licensed in the same jurisdiction	A US biosimilar must be compared with an RP licensed in the US	An EU biosimilar must be compared with an RP licensed in the EU
Nomenclature[a]	Standardized INNs should be used to identify an RP, followed by a four letter suffix to identify its biosimilar (eg, etanercept and etanercept-szzs)	As per WHO guidelines	Proprietary names should clearly distinguish between the RP and its biosimilar without indicating similarities (eg, the RP for etanercept is Enbrel and its biosimilar is Benepali)
Interchangeability	No formal demonstration of interchangeability is required	Interchangeability must be demonstrated in ≥1 clinical study involving ≥3 switches between the biosimilar and its RP	No formal demonstration of interchangeability is required
Biosimilar/RP switching policy	No specific recommendations; individual member states should make their own policies	Refer to "The Purple book" (a comprehensive list of biologics with information on biosimilarity and interchangeability)	Each biosimilar is unique; refer to molecule-specific guidance documents

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; INN, International Non-proprietary Name; RP, reference product; WHO, World Health Organization.
[a]Individual countries often develop their own systems.

present early experience in rare diseases following the introduction of NCBTs for Gaucher disease (GD) and consider the wider implications for the treatment of rare diseases.

1 | NON-COMPARABLE BIOTHERAPEUTICS ARE NOT BIOSIMILARS

Biosimilars and NCBTs may differ from the RP across a variety of important structural and functional elements including glycosylation and purity. However, unlike for biosimilars, approval of NCBTs (also known as "biomimics" or "intended copies") is usually based on "short-cut" regulatory pathways where limited clinical and comparability data to a RP is considered. In this situation, these differences may have important implications for drug efficacy and patient safety.[4] For example, NCBTs for recombinant erythropoietins have been associated with adverse immunological effects leading to pure red cell aplasia (PRCA).[5] Furthermore, whereas WHO, FDA and EMA biosimilar guidelines require the use of a unique naming system that enables prescribers to distinguish between a biosimilar and its RP (Table 1), short-cut regulatory pathways for NCBTs may permit the use of the same International Nonproprietary Name (INN) for the NCBT and its RP. This could cause confusion over exactly which drug HCPs are prescribing and it may result in inadvertent substitution and adverse event reporting. HCPs and patients — especially those with chronic, progressive diseases with irreversible complications such as rare genetic diseases — have to be aware that NCBTs should not be considered biosimilar to their RP.

2 | GAUCHER DISEASE (GD), A RARE DISEASE EXAMPLE

Gaucher disease is a rare, inherited lysosomal storage disease that affects 1 in 40 000 to 60 000 people, depending on ethnicity.[6] It is caused by biallelic mutations in the gene that encodes lysosomal glucocerebrosidase (GBA). It is characterized by an accumulation of glucosylceramide in macrophages of the liver, spleen and bone marrow leading to multiple manifestations, including hepatosplenomegaly, anemia, thrombocytopenia, growth retardation and skeletal disease. Three types of GD exist; GD types 2 and 3 can be distinguished from type 1 by the presence of CNS involvement. Gaucher disease is progressive, with long-term complications such as osteonecrosis and malignancy. Clinical and radiological evidence of diverse bone involvement occurs in the majority of patients even in the absence of significant hematological and visceral abnormalities, underscoring GD heterogeneity and the need for long-term monitoring.

Gaucher disease type 1 was the first disease to be successfully treated with Enzyme Replacement Therapy (ERT), initially in 1991 with placental-derived glucocerebrosidase (alglucerase, Ceredase®, Genzyme

Corporation, Cambridge MA, USA), and beginning in 1994, with recombinant glucocerebrosidase (imiglucerase, Cerezyme®, Genzyme Corporation, Cambridge, MA, USA). In addition to Cerezyme, two other ERTs are currently available for the treatment of GD in the USA and/or Europe, (a) VPRIV® (velaglucerase alfa, Shire Human Genetic Therapies, USA) and (b) Elelyso® (taliglucerase alfa, Pfizer, New York, NY, USA). There are as well as two small molecule substrate reduction therapies (SRT), (a) Cerdelga® (eliglustat, Genzyme Corporation, Cambridge, MA, USA) and (b) Zavesca® (miglustat, Actelion Pharmaceuticals, San Francisco, CA, USA).[6]

The effectiveness of ERT for Gaucher disease requires selective, mannose receptor-mediated uptake of enzyme into target cells. This selective uptake into the correct cells depends on the carbohydrate profile of the enzyme preparation. Glucocerebrosidase is a glycoprotein comprising four covalently bound oligosaccharide chains attached to amino acid side chains, of which one oligosaccharide is an oligomannose. Therapeutic targeting of recombinant GBA to glucosylceramide-laden macrophages is dependent on mannose receptor-mediated endocytosis via these terminal mannose residues. However, GBA has other terminal carbohydrate residues that recognize receptors on other cell types. Therefore, from a therapeutic perspective, the relative terminal mannose residue content is a critical protein quality attribute that drives a structure-function relationship and potentially modulates the effectiveness of ERT. The glycosylation profile of recombinant proteins may be impacted by aspects of the manufacturing process (eg, the cell line in which the protein is produced), some of which are designed to modify protein targeting and are therefore proprietary.[7] This is taken into account for the approval of biosimilar medicines, but not for the approval of NCBTs.

In addition to the currently available ERTs for the treatment of GD, three other ERTs have been approved outside of the USA/EU with the INN imiglucerase: (a) Abcertin® (imiglucerase, ISU Abxis, South Korea) has been approved so far for use in countries such as South Korea, Iran, Bolivia and Kazakhstan based on regulatory pathways that do not fulfill WHO requirements for the development/approval of a biosimilar (Table 2); (b) Asbroder™ (imiglucerase) is approved as an orphan drug in Mexico. No scientific literature or clinical trial information is published for Asbroder; however, the active substance for both Asbroder and Abcertin is manufactured by ISU Abxis. Despite using the same INN as Cerezyme, Asbroder does not meet the WHO definition of a biosimilar.[8] (c) Very recently, Glurazyme® (imiglucerase, Generium Pharmaceutical, Russia) has been approved in Russia according to local biosimilar regulations and is therefore considered interchangeable with its RP in Russia. However, no data has been published or presented for this product.

Abcertin was initially approved in South Korea in 2012 via a national pathway that permitted the submission of phase 3 data after approval, and outside of approval pathways for biosimilars and other orphan drugs. It was approved based on the results of three clinical studies: a 5-day, double-blind, placebo-controlled Phase 1 dose-escalation study conducted in 24 healthy volunteers (NCT01881633); a 24-week prospective, Phase 2, open-label switch-over study in one adult and four children/adolescents with confirmed GD type 1 previously treated with Cerezyme; and a post-approval, 24-week, Phase 3 trial in 7 treatment-naïve children with GD type 1.[9,10] Studies providing a direct comparison to the RP, Cerezyme, and physicochemical, immunological, or structural data have not been presented. A Phase 3 head-to-head trial comparing Abcertin and Cerezyme was withdrawn before recruiting subjects (NCT01161914).

TABLE 2 Considerations for the development of biosimilars for rare diseases: lessons learned from Gaucher disease

Characteristic	Implications for the development of biosimilars for rare diseases
Size of clinical studies	Recruitment of sufficient numbers of patients for clinical/equivalence studies may be particularly challenging due to disease rarity; long patient recruitment times may be necessary to ensure sufficient numbers
Clinical study duration/ follow up	The progressive nature of genetic disorders means long-term follow-up and evidence-building is necessary to assess the longitudinal effects of treatment on outcomes that emerge later in life
Clinical study population	The precise clinical manifestations and disease courses for genetic diseases depend on disease subtype, age of onset, the precise mutation, and levels of residual protein activity. Populations must be clearly defined to enable a comparison of data across treatment groups/ studies
Direct comparison with an RP	In vitro analytical testing and nonclinical studies are required to demonstrate pharmacological, toxicological, and pharmacokinetic equivalence to the RP[1-3]
Molecular structure	Subtle changes in post-translational modifications (eg, glycosylation) due to variations in the manufacturing process may have a major impact on pharmacokinetics/ pharmacodynamics, safety, immunogenicity, and efficacy; structural data should be obtained by regulatory authorities for all biosimilars to ensure they are sufficiently similar to the RP
Immunological and long-term safety data	Immunogenicity and safety should be confirmed in one or more phase 3 studies involving patients with at least one relevant indication. Biosimilar pharmacovigilance programs should be separate to those for the RP

Abbreviation: RP, reference product.

Authors of the Phase 2 study initially referred to Abcertin as a "biosimilar" for Cerezyme.[9] Although they have since corrected their claim in an erratum to their initial publication, confusion could persist regarding the precise nature of Abcertin.[10] This is partly because its prescribing information includes safety and efficacy data from Cerezyme's clinical trials without indicating that the experience is not based on clinical use of the Abcertin product, and partly because the manufacturer adopted the INN imiglucerase without complying with WHO naming guidelines.

As a result, HCPs and patients could be misled into believing that different ERTs using the same INN, in this case imiglucerase, are the

same or biosimilar, that they have equivalent efficacy and safety data, and that they are interchangeable. Potential consequences may include inadvertent switching and substitution between drugs, resulting in challenges in assessing the safety profile and creating the risk for inaccurate reporting of each drug's adverse events. In addition, given the progressive nature of the disease, the potential differences in clinical benefit for the patient might be visible only after a longer treatment period, particularly for bone disease.

3 | DISCUSSION AND CALL TO ACTION

Recent experience from the approval of NCBTs for GD, which use the same INN, highlights the considerations that should be taken into account during the development, regulatory approval and use of biosimilars for rare diseases (Table 2). Firstly, rare diseases such as GD have small numbers of patients with a wide range of genotypes and phenotypes. Consequently, clinical studies need to be carefully designed to obtain sufficient comparable data for the biosimilar and its RP, as per guidelines of EMA, FDA or WHO. Secondly, like many rare diseases, GD is a chronic, progressive disorder that may lead to a number of long-term irreversible complications if not treated optimally. The systematic collection of long-term real-world evidence, as is done in the International Collaborative Gaucher Group (ICGG) Gaucher Registry, has continued to shed light on the natural history of Gaucher disease. The registry has also improved understanding of the long-term effectiveness of therapy; long-term real-world data collection should be a requirement for any drug developed for rare diseases. Thirdly, glycosylation profiles should be fully characterized for all biologics, as this can contribute to their immunogenicity, potency, specific activity and biodistribution.[7] An additional critical consideration is the use of a unique naming identifier that differentiates between biologic products to ensure traceability, and to avoid confusion at the prescribing and dispensing level as well as among patients.

There is an urgent need for improved education and awareness among HCPs, and patients involved in rare diseases, on the differences between RPs, biosimilars and NCBTs, including regulatory requirements, terminology and requirements for long-term monitoring. Responsibility for this lies with industry, medical societies/institutions and patient advocacy groups. Physicians should be vigilant of product information sources and ensure that the therapies their patients receive meet global standards. All stakeholders, including healthcare providers, patients, regulatory authorities and industry, should provide input on the establishment and revision of public policies relating to biosimilars.

Regulators should insist that transparent product labelling and unique nomenclature is used for biologics and the long-term efficacy monitoring and safety reporting through observational and pharmacovigilance databases are implemented. Manufacturers of biosimilars have a responsibility to provide and publish high quality data that demonstrate similarity between the proposed biosimilar and its RP, and to ensure long-term real-world safety and efficacy data collection. Without this oversight, continued introduction of NCBTs, and/or use of the same INN, may expose vulnerable patient populations, including those with progressive rare diseases, to a risk of disability, impaired quality of life, and ultimately to increased costs of treatment.

In summary, consistent adoption of global regulatory standards (WHO, FDA or EMA), including unique naming, is urgently required across all countries for all biologics, without exception. This will ensure that all NCBTs are, in fact, biosimilars. The specifics of rare diseases and the unique challenges associated with the development of orphan biologics may suggest the need for the development of specific biosimilar guidelines for rare diseases.

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CONFLICT OF INTEREST

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REFERENCES

1. World Health Organization. Regulatory Expectations and Risk Assessment for Biotherapeutic Products 2014. https://www.who.int/biologicals/WHO_Risk_Assessment_for_Biotherapeutics_1st_PC_24_Jan_2014.pdf. Accessed June 2019.
2. United States Food and Drug Administration. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance for Industry 2015. https://www.fda.gov/media/82647/download. Accessed June 2019.
3. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP).CHMP/437/04 Rev 1. Guideline on similar biological medicinal products 2014. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf. Accessed June 2019.
4. International Federation of Pharmaceutical Manufacturers & Associations. IFPMA policy statement on non-comparable biotherapeutic products 2014. https://www.ifpma.org/wp-content/uploads/2016/02/Non-comparable_Biotherapeutic_Products__English__02.pdf. Accessed June 2019.
5. Ebbers HC, Crow SA, Vulto AG, Schellekens H. Interchangeability, immunogenicity and biosimilars. *Nat Biotechnol*. 2012;30:1186-1190.
6. Valle D, Beaudet AL, Vogelstein B, et al. *The Online Metabolic and Molecular Bases of Inherited Disease*. New York, NY: McGraw Hill Companies Inc; 2018:146.
7. Sola RJ, Griebenow K. Glycosylation of therapeutic proteins: an effective strategy to optimize efficacy. *BioDrugs*. 2010;24:9-21.
8. Castañeda-Hernandez G, Carbajal-Rodriguez L, Ceron-Rodriguez M, et al. Are there biosimilar orphan drugs for Gaucher disease? An overview in Mexico. *GaBi J*. 2019;8:1-5.
9. Lee BH, Abdalla AF, Choi JH, et al. A multicenter, open-label, phase III study of Abcertin in Gaucher disease. *Medicine*. 2017;96:e8492.
10. Choi JH, Lee BH, Ko JM, et al. Erratum: A phase 2 multi-center, open-label, switch-over trial to evaluate the safety and efficacy of Abcertin® in patients with type 1 Gaucher disease. *J Korean Med Sci*. 2015;30:1373.