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BIOSIMILAR RECOMBINANT PROTEIN THERAPEUTICS

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ABSTRACT
Recombinant protein therapeutics were first introduced in the 1980s. Patents for many approved recombinant protein therapeutics have either expired or are about to expire. Thus the market is open for generic versions, referred to as 'biosimilars' (European Union) or 'follow-on protein products' (United States). Biosimilars offer one way of widening access and enabling better value to be obtained from the money spent on healthcare. Current analytical methods cannot characterise biosimilar recombinant protein therapeutics sufficiently in order to confirm structural equivalence with reference products due to their complex high-molecular-weight three-dimensional structures, thus the term biosimilar rather than generic is used. In addition, recombinant protein therapeutics are produced by living cells, production and purification methods can affect folding/glycosylation profile in the biosimilar product compared to the reference product.The foundation of approval for a new recombinant protein therapeutic by major regulatory bodies is traditionally a large clinical program to test safety and efficacy of a novel treatment. By contrast, the foundation of approval for a biosimilar recombinant protein therapeutic is a large analytical program to test similarity in molecule structure to the previously approved reference product. The regulatory approval pathways for biosimilar and biobetter (improved version) of therapeutic products are different and the sponsors of the application for a new product must decide which route they need to take prior to submitting their application. Data from pre-authorisation clinical studies are usually insufficient to identify long term/rare adverse effects. Therefore, clinical safety of biosimilars must be monitored closely on an ongoing basis during the post approval phase including continued benefit-risk assessment. Any specific safety monitoring imposed on the reference medicinal product or product class should be adequately addressed in the pharmacovigilance plan of the biosimilar. There is a rapid change in biosimilar market and legislation due to several unresolved issues, including substitution, naming and labelling. Postmarketing pharmacovigilance can certainly help in addressing some of these issues. Greater awareness of the potential differences between products will enable pharmacists to play a very important role in providing information for both prescribers and patients in order to insure the safe, effective and cost-effective use of biosimilars.

KEYWORDS: Biosimilars, generics, biobetter, pharmacovigilance.

INTRODUCTION
At present, many different recombinant proteins or peptides are available for clinical use by the US Food and Drug Administration (FDA)/the European Medicine Agency (EMA) and many more are in development, Main pharmacological categories of recombinant protein therapeutic are presented in table 1.[1]

Table 1: Main pharmacological categories of available recombinant protein therapeutics.[1]

Pharmacological classification	Examples
Hormone-based products	Recombinant insulins, glucagon, gonadotropins and human growth hormone
Haematopoietic growth factors	Erythropoietins and colony stimulating factors
Recombinant blood factors	Factors VIIa, VIII and IX
Recombinant cytokines	Recombinant interferons, interleukins and other cytokines.
Recombinant thrombolytics	Tissue plasminogen activator based products
Enzyme-based products	Recombinant DNase
Subunit vaccines (containing a	Recombinant hepatitis B subunit vaccines

recombinant antigenic component)	
Others include	Antibody-based products (used for in vivo diagnostic and therapeutic purposes).

The patents of a growing number of recombinant protein therapeutics such as recombinant human erythropoietins (Epoetins), recombinant human insulin and recombinant human growth hormones, have already expired, which has led to an increased interest in the development of generic versions, referred to as 'biosimilars'(European Union) or 'follow-on protein products' (United States). The regulated introduction of biosimilars into the market has been forecasted to increase access to much needed biologic medicines and reduce costs.[2,3]

Major regulatory bodies such as the world health organization (WHO), the EMA and the FDA agree that a Biosimilar recombinant protein therapeutic is highly similar but not identical to the reference product, in terms of safety, purity, and potency of the product.[3,4,5] The "reference product" is the "single recombinant protein therapeutic product licensed in the relevant country, against which a potentially biosimilar recombinant protein product is evaluated."

STRUCTURE OF PROTEIN THERAPEUTICS

Proteins have complex structures, in general proteins can differ in at least three ways:
(1) primary amino acid sequence;
(2) modification to amino acids, such as sugar moieties (glycosylation) or other side chains; and
(3) higher order structure (protein folding and protein-protein interactions).

Biosimilar recombinant proteins should have the same primary amino acid sequence with the reference product and should have the same number/sites/types of glycosylation, and are expected to have very similar folding and glycosylation levels to the reference product, the slight variation in folding or glycosylation pattern is permitted provided it does not affect safety and efficacy of the product.[5,6,7]

Expression systems for recombinant proteins include bacteria, yeast, insect cells, mammalian cells, and transgenic animals and plants. The system of choice can be dictated by the cost of production or the modifications of the protein (for example, glycosylation, phosphorylation or proteolytic cleavage) that are required for biological activity.[8] recombinant Protein modifications and higher order structure can also be affected by formulation and environmental conditions, including light, temperature, moisture, packaging materials, container closure systems, and delivery device materials.[5,6]

The native human Erythropoietin (EPO) structure is described here as an example in order to illustrate the complex nature of recombinant protein therapeutics. EPO is a glycosylated protein hormone and a haematopietic growth factor produced mainly in the kidneys. The mature Protein has 165 amino acids, two disulfide bonds, and three N- and one O-linked carbohydrate chains. EPO is heavily glycosylated, which increases the molecular weight from 18.4 kDa for the unglycosylated molecule to approximately 34 kDa, EPO requires glycosylation for its in vivo biological activity.

Biosimilar Epoetins are produced commercially by the expression of erythropoietin cDNA clones in Mammalian cell lines, most commonly in Chinese hamster ovary, baby hamster kidney, and human cell lines.[8] The recombinant material is homogenous with respect to the peptide sequence of natural erythropoietin, number and type of glycosylation sites but the glycosylation profile (the degree of glycosylation at the glycosylation site) appear to differ between preparations.[5,6,7] Regulatory authorities allow for small variation in the glycosylation profile of Epoetins. Several biotechnology laboratories are producing biosimilar Epoetins for clinical purposes, it is well recognised that the type of host cell line used for its production, culture conditions employed and purification process applied, may all affect the glycosylation profile, folding pattern of the preparation and thus influence the final bio potency of the biosimilar Epoetins.[8-11]

REGULATING BIOSIMILARS

The EMA was the first major regulatory authority to implement a framework for the marketing authorization of biosimilars in 2005,[5] and has one of the most detailed and stringent guidelines for developing biosimilars. Since the introduction of a regulatory mechanism for developing, reviewing and approving biosimilars, The EMA has updated its overreaching guidance on the general principles of biosimilar development, quality and nonclinical and clinical issues. In addition, class specific guidelines for several biosimilars have been developed, such as biosimilars to growth hormones, monoclonal antibodies, Granulocyte colony stimulating factors (G-CSFs), recombinant follicle stimulating hormones, interferons, low molecular weight heparins and recombinant insulin.[12-16]

In 2009 the WHO developed a set of globally accepted standards to assure the safety, efficacy and quality of biosimilar medicines. These have been developed in the wake of increased interest in biosimilars by local regulatory authorities seeking to develop national standards.[10]

Some emerging markets have developed their own regulatory pathways for biosimilars, hoping to meet a growing demand for biologic medicines, for example Singapore and Malaysia amended their guidelines mainly in accordance with the EMA guidelines, while Brazil and

Cuba chose the WHO and Canadian guidelines as the basis for developing regulations.[2]

In March 2010, the U.S. biosimilar pathway was signed into law as part of the Affordable Care Act. In April 2015, the Food and Drug Administration (FDA) issued one of their most recent guidance documents on biosimilar product development, in order to assist industry in developing such products in the United States.[6] In their latest guidance the FDA recommends that sponsors use a stepwise approach to developing the data and information needed to support a demonstration of biosimilarity.[6]

Before marketing authorization is granted by regulators such as the FDA or the EMA, for a biosimilar product, the originator company and the biosimilar manufacturer must provide substantial data to show that the biosimilar product is sufficiently similar to the original product.[7]

Overall, the biosimilar must demonstrate that it has no significant clinical differences to the reference product, but some limited variation is permitted. This is because biosimilar approval is based on a demonstration of similarity to a previously approved originator product rather than a de novo demonstration of safety and effectiveness.[8-10]. If the biosimilar comparability exercise indicates that there are relevant differences between the biosimilar and the reference medicinal product, making it unlikely that biosimilarity will eventually be established, a standalone development to support a full Marketing Authorisation Application for a biobetter (that is an improved version of the reference product), should be considered instead.[6,7] A biobetter is more different from an originator product than a biosimilar would be, even though a biosimilar cannot itself be an exact replica of the reference product. In many cases a biobetter recombinant protein therapeutic is designed to have desired properties which are lacking in the reference product.

Several examples of biobetter recombinant protein therapeutics have been approved by FDA/EMA, such as various insulin analogues with different primary amino acid sequence and folding from recombinant human insulin. Another example of biobetter recombinant protein therapeutic is produced by adding a polymer to the recombinant protein, table 2.

Table 2: Examples of biobetter recombinant protein therapeutics.[2]

Reference product	Examples of Biobetter product/s
Insulin	Insulin analogues: fast-acting insulins such as insulin lispro, insulin aspart and insulin glulisine.
Erythropoietin	Darbepoetin-α: an erythropoietin analogue, synthesized with five rather than three N-linked carbohydrate chains; this modification causes the half-life of darbepoetin to be threefold longer than that of erythropoietin.[12]
Filgrastim	PEG filgrastim: filgrastim protein fused with polyethylene glycol (PEG), which gave it the ability to stay in a patient's body longer (improved bioavailability)

SUBSTITUTION AND PHARMACOVIGILANCE

Recombinant protein therapeutics tend to be more immunogenic than traditional small-molecule drugs due to their complex nature and size.[18] Although the immunologic reactions that most recombinant protein therapeutics trigger tend to be relatively harmless, there have been cases in which the unexpected immunogenicity of a new or approved drug has caused severe injury or death.[17-19] The onset and incidence of immunogenicity is unpredictable; therefore, extended postmarketing surveillance (pharmacovigilance) to monitor potential immunogenicity is very important.[27]

In order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified." Substitution of biosimilars with their reference biological products can result in problems, such as lack of traceability in the case of an adverse event,[18] if substitution has taken place, the doctor may not know which brand was used and so only the International Non-proprietary Name (INN) can be included in the adverse event report. This lack of traceability may prevent identification of the particular product responsible for the adverse reaction.

CONCLUDING REMARKS

Biosimilars present new set of challenges for regulatory authorities when compared with conventional generics. While the demonstration of a pharmacokinetic similarity is sufficient for conventional, small-molecule generic agents, a number of issues makes the approval of biosimilars more complicated and more costly compared to generic drugs.

The amount of data needed to demonstrate that the new product is highly similar to the reference product, depends on the complexity of the reference product. The degree of demonstrated similarity to the reference product will normally influence the range of clinical trials required by regulatory authorities which means biosimilar manufacturers must invest in clinical trials as required by the regulators in addition to manufacturing and post-approval safety monitoring programs similar to that of the original innovator companies. Because of this investment, cost savings achievable with biosimilars may not be as great as can be experienced with small molecule generics.

It is interesting to note that up to October 2014, twenty biosimilar recombinant proteins have been approved by the EMA, three quarters (fifteen biosimilars) are biosimilars to only two recombinant proteins (Erythropoietin and Filgrastim). It is possible that after the first successful biosimilar application for a reference recombinant protein therapeutic, subsequent applicants for biosimilars to the same reference product, to the same regulatory authority will have a better idea of the amount of work required in order to get approval of a new biosimilar application. Biosimilars and biobetters follow entirely different licensing pathways. If a company is developing a biobetter, then the regulatory process is much longer and much more expensive than developing a biosimilar product, but the financial gains from marketing a new patented product is expected to be better than marketing biosimilar, in particular in wealthy countries which have highly regulated markets like the U.S. When prescribing biosimilar protein therapeutics, it is good practice to use the brand name. This will insure that automatic substitution of biosimilar medicine does not occur when the medicine is dispensed. As adverse reaction reports need to clearly state the brand of suspected biosimilar therapeutic.

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