

A Primer on Biosimilars: FDA-Approved and those in the Pipeline

Gopalakrishna Pillai^{1*}, Daniel R Malcom² and Arthur Cox¹

¹Department of Pharmaceutical Sciences, Sullivan University College of Pharmacy, Louisville, Kentucky, USA

²Department of Clinical and Administrative Sciences, Sullivan University College of Pharmacy, Louisville, Kentucky, USA

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*Corresponding author: Gopalakrishna Pillai, Sullivan University College of Pharmacy, 2100 Gardiner Lane, Louisville, KY 40205, USA ; Tel: 502 413 8951; Fax: 502 515 4669; E- mail: gpillai@sullivan.edu

Abstract

Biologics have made groundbreaking treatments possible, for several difficult to treat conditions. However, they are very expensive, and biosimilars are expected to push prices down like the generics of small molecule drugs did in the past, replacing more costly brand-name drugs. Biosimilars are not just generic replacement for brand name biologics, and their effect on cost reduction will be much more modest. Biologics, made from living organisms, are much larger in size and complex molecules than small molecule drugs which are easily synthesized, characterized and copied. Biosimilars may be highly similar to the original licensed biologic product but not a fingerprint copy; therefore, some differences are expected. This article describes the criteria for establishing similarity and interchangeability, current regulations and the clinical and pharmacoeconomic aspects of the four FDA approved biosimilars in 2015 and 2016.

Key words: Biosimilars; Biobetters; Interchangeable biologics; Naming Biologics; Quality attributes; FDA approved Biosimilars; Regulations; Pharmacoeconomics.

Introduction

Many important medications, such as monoclonal antibodies and vaccines, are derived from biological components. They are made from living organisms, including humans, other animals, and microorganisms. Biological products are used to treat some of the most serious and previously difficult to treat conditions, such as inflammatory bowel diseases, rheumatoid arthritis, anemia, and various forms of cancer. Biological products differ from small molecular drugs in several important ways [1]. First, they are generally large, complex molecules with molecular weight of upwards of 150,000 Daltons, including proteins with as many as 1,300 amino acids. Conventional small-molecule drugs are of relatively low molecular weight (100-1000 Da), are typically made from pure chemical substances, and have easily identified (and duplicated) structures. In contrast, biological products have complex structures that are often not easily identified and characterized. Their structures and properties are also sensitive to changes in production process. Biologics are also a major cost-driver for health care, accounting for nearly 20% of worldwide spending on pharmaceuticals [2].

There are three types of biological products relevant to the current discussion: biosimilars, interchangeables, and so-called "biobetters." They are similar in intended activity, such as receptor agonism or enzyme inhibition, but not completely identical in all pharmacologic, pharmacokinetic, and pharmacodynamic properties to the original product.

Every biological or biopharmaceutical product displays a certain degree of variability, even between different batches, which is due to the inherent variability of the biological expression system and the manufacturing process [3].

Biosimilar antibodies are "generic" versions of the originally marketed antibodies. The originally marketed versions have been termed "innovator" (or "originator") antibodies. Both the innovator and biosimilar versions contain the same amino acid sequence, but are produced from different clones and manufacturing processes. Therefore, biosimilar monoclonal antibodies (mAbs) may have differences in their chemistry, such as glycosylation and surface charge that may affect quality, safety, pharmacokinetics, and potency [4,5].

Unlike the low-cost generic versions of small molecules that are off-patent and for which exact copies can be produced, it is currently not possible to produce exact copies of large proteins and glycoproteins, such as antibodies, because of their structural complexity and inherent potentially immunologic activity (e.g., infusion-related reactions to monoclonal antibodies). Therefore, the term "biogeneric" is not an accurate description of biosimilars. The current U.S. construct of "generic" medications emerged with the passage of the Hatch-Waxman Act of 1984 [6], which allows manufacturers the ability to submit "abbreviated new drug applications" to gain approval to market a version of a comparator product. The "generic" version is required to have the same active ingredient, administration route, dosage form, and strength as the comparator product. Under this mechanism, manufacturers are not required to submit additional efficacy or safety studies, only data supporting their "bioequivalence" to the reference product. Given the complexities of biologic products, duplication of the medications is not possible to the standards required by Hatch-Waxman. However, with new techniques of bioprocessing and analytical methods, it is possible to produce proteins and glycoproteins that are "similar," but not identical, to

reference products.

Biosimilars are “highly similar” to an already approved biological product (known as the reference product) and have been shown to have no clinically meaningful differences from the reference product in terms of safety and effectiveness. The biosimilar has the same mechanism of action, route of administration, dosage form, strength, and same indications of use as the reference product. An *interchangeable* product must meet the additional requirements that it must produce the *same clinical results* as the reference product in any given patient. Additionally, the risk in terms of safety and the effectiveness of alternating or switching between the interchangeable and the reference product should not be greater than the risk of using the reference product itself. A biosimilar product can be prescribed by a health care provider in place of a reference product therapeutically, whereas an interchangeable product may be substituted (dependent on state law) for the reference by a pharmacist without the intervention of the health care provider who prescribed the reference product.

It must be emphasized that biosimilars are not the same as generic drugs. Generic versions of small molecule drugs have well-defined structure, are relatively easily synthesized, and are exact copies of brand-name drugs and, therefore, bioequivalent and interchangeable. Biosimilars are biological products that are highly similar to reference product but have “allowable differences” due to the complex and variable chemical structures produced by living organisms [7]. It is quite difficult to produce a copy of a biological product that is identical in all respects.

A third group, besides the biosimilars and interchangeables, are called “*biobetters*.” Like the biosimilars, these are also being marketed and referred to as “follow-on” pharmaceuticals. Biobetter antibodies are antibodies that target the same epitope (site on the antigen where binding with an antibody occurs) as a marketed antibody. However, they have been engineered to have improved properties. For example, engineering the Fc domain to increase the serum half-life, optimizing glycosylation pattern to enhance effector functions, PEGylation, altering formulation, and making delayed release complexes [8, 9].

Biobetter antibodies then become new molecular entities since they are too dissimilar to be recognized as biosimilar. One example is Centocor’s new anti-TNF product golimumab, marketed as Simponi. The original product (infliximab) was highly immunogenic; however, the biobetter has reduced undesirable effects because it is humanized [10]. Controlled and optimized glycosylation have been obtained in glyco-engineered CHO (Chinese hamster ovary) cells or yeast strains. For example, copies of rituximab and trastuzumab amino acid sequences have been produced with afucosylated glycoforms, resulting in a 40- to 100-fold increases in antibody-mediated cellular cytotoxicity (ADCC) [11,12]. Increased plasma half-life can also be achieved, such as in copies of rituximab, trastuzumab, and bevacizumab with a mutation of 2-3 amino acids in the Fc domain [13]. A biobetter version of cetuximab produced in CHO cells is currently

in development in China [14].

The biobetters are handled as innovator molecules, so similar regulatory standards are applicable. Unlike generic small molecule drugs, the development expense is very high for biosimilars and biobetters (up to \$100-250 million per molecule) [15].

Table : Biosimilars approved by the US FDA in 2015-2016

Date of approval	Biosimilar product	Original (reference) product
March 6, 2016	Filgrastim-sndz/ Xarxio	Filgrastim/Neupogen
April 5, 2016	Infliximab-dyyb/ Inflectra	Infliximab/Remicade
August 30, 2016	Etanercept-azzs/ Erelzi	Etanercept/Enbrel
September 23, 2016	Adalimumab-atto/ Amjevita	Adalimumab/Humira

How is biosimilarity or interchangeability determined?

Biosimilarity and interchangeability is determined based on matching all the “critical quality attributes” between a reference product and the biosimilar candidate. A deep understanding of the critical quality attributes of a reference product is fundamental to producing a high-quality biosimilar. Rational evaluation must be made of how each attribute, alone and in concert with other attributes, impacts safety, efficacy, pharmacokinetics and overall quality [16].

Critical quality attributes

There are several attributes that must be carefully considered for each biological product. Some of these attributes are important because they determine how the body recognizes them. As a result, they are critical to the safety, efficacy, and pharmacokinetics of the drug. Characteristics important to these parameters are known as “critical quality attributes” [17]. These include the chemical structures, which are determined by the DNA template used, the cell line, and the manufacturing process. A biosimilar will not be exactly like its reference product, and some features will not match; however, the critical quality attributes need to match to ensure that the biosimilar medicine and the original biologic work in the same way for every patient.

In addition to the critical quality factors, biologics generally have two other types of attributes: (1) those known to be unimportant to their function and (2) those with uncertain relevance. One complicating factor in biosimilar development is determining which attributes are most important in cases where the biology is unclear. This epitomizes the difficulty in the development of biosimilars; as many as 100 attributes of a reference product may be considered for matching to produce a high quality biosimilar.

Characterization of monoclonal antibodies

Several analytical methods are used to determine the physicochemical properties and molecular structure of monoclonal antibodies. Since they are glycoproteins, determination of the glycosylation pattern is important for new as well as biosimilar mAbs [18]. Glycosylation pattern will have an impact on the pharmacokinetics and pharmacodynamics of mAbs. Most therapeutic mAbs are derived from IgG and contain a glycosylation site in the Fc region at amino acid position 297, and in some cases in the Fab region. For Fc fusion proteins, glycosylation also occurs in the fusion partners. Depending on the host, the glycosylation pattern can be significantly different. Glycans that have a major impact on PK/PD of mAbs include mannose, sialic acid, fructose and galactose [19].

In terms of the molecular structure and function, high mannose-type glycans are often a critical quality attribute [20]. This attribute impacts on the amount of time the drug stays in the body, and can also be important for determining how a biological medicine functions and treats a specific disease. Afucosylated-type glycans are sometimes critical quality attributes [21]. Depending on the biological medicine and the disease being treated, this attribute may be important, not important, or of unknown importance to biological function. When it is not determined that if the attribute is important, biosimilars should match the attribute to limit risk to the patient. The last amino acid that a cell adds to an antibody remains there only temporarily and is later removed by the cell. It is acceptable for a biosimilar to have differences in this amino acid, as it does not impact how the antibody functions or how it moves through the body.

Clone identification

Due to their complex nature, biologics are produced by cells and later purified. Different cells will produce slightly different biologics. Therefore, thousands of cells are evaluated to select a clone that will produce the product that is most similar to the reference product. Transfection (insertion of the biologic's DNA in to the host cell to create large number of clones) and amplification (addition of another agent to create additional DNA to produce greater amount of biosimilar per cell) is the next step [22]. Process optimization then requires in-depth analysis of cell growth conditions, separation of the biosimilar, and further refinement.

Clinical development

Development of the biosimilar can be abbreviated because of the in-depth understanding of the reference product. In general, two phases of clinical studies are required: phase I studies to demonstrate similar pharmacokinetics and pharmacodynamics and phase III studies to demonstrate similar efficacy, safety, and immunogenicity to the reference biologic [23]. The following evidence is required for comparison with a licensed reference product: structure, function, nonclinical studies (animal studies and toxicity assessment), human PK/PD, clinical safety, clinical effectiveness, immunogenicity and pharmacovigilance [24-27].

Regulatory guidelines

The European Medicines Agency (EMA), which regulates pharmaceuticals for countries of the European Union (EU), established the first legal regulatory guidelines for "similar biological medicinal products" (i.e. biosimilars) in 2005. These guidelines require the demonstration of similarity by performing side-by-side comparison against the originator product. In addition to general guidelines, product-specific details were also published for a variety of molecules including monoclonal antibodies. Several of the original guidelines have been or are in the process of being revised. All guidelines plus current revision concept papers and drafts are available on the EMA biosimilars website [28]. The first biosimilar molecule approved in the EU in April 2006, was Omnitrope, a version of somatotropin. The protein structure of Omnitrope is well characterized: it is not glycosylated, the mechanism of action is known, and its safety and efficacy profile is well-documented [29]. As of 2016, the EU has approved 22 applications, and is continually updating its guidelines, both general and product-specific [30].

Initially, the biosimilars approved were simple endogenous proteins such as somatotropin, epoetin, and filgrastim. The challenge of establishing biosimilarity of the more complex and larger molecules such as monoclonal antibodies is much greater than that of smaller molecules. The first biosimilar mAbs approved in Europe in June 2013 were versions of infliximab (Remsima [Celltrione] and Inflectra [Hospira]). The drug companies Celltrion, Sandoz, and several other leading drug developers have more biosimilar mAbs currently in late-stage clinical trials [31].

In the US, the Biologics Price Competition and Innovation Act (BPCIA), enacted in 2009, provides a regulatory approval pathway for biosimilars – the 351(k) route of the Public Health Service (PHS) Act [32]. This pathway also requires the comparison of a biosimilar molecule to a single reference product which has been approved under the normal 351(k) route in terms of safety, purity and potency. There is also a provision for two levels of product – "biosimilar" and "interchangeable biosimilar" [33]. As discussed previously, an "interchangeable" biological product is one that may be substituted (pursuant to state law) for the reference product without the direct authorization of the prescriber. Therefore, more robust data, including clinical switching studies, are required if a product is to be labelled as interchangeable.

The US Food and Drug Administration (FDA) has published multiple guidance documents to assist biosimilar developers [34]. These relate to scientific considerations in demonstrating biosimilarity, quality considerations, clinical pharmacology data required, and reference product exclusivity, among other topics. The most recent draft guidance was issued in January 2017 related to interchangeability with a reference product [35]. To date, no product has been approved as "interchangeable" under the new pathway. With the new FDA guidance, however, that may soon change.

Importantly, both the European and US regulatory pathways depend on the ability to demonstrate biosimilarity, involving rigorous comparison against batches of originator product. This occurs initially at the physicochemical level, then through appropriate comparative safety and efficacy tests.

In an effort to protect the patents of biologics in the same manner as small molecule drugs, the BPCIA established a twelve year period of exclusivity from date of first licensure during which a biosimilar or interchangeable product may not be licensed under 351(k) [36]. This includes a four-year period when an application may not be reviewed by the FDA [37]. Given the significant cost and presence of biologic products, payers and third party insurance plans are anxiously awaiting to determine what, if any, impact biosimilars will have on “bending the cost curve” related to biologics.

FDA has also recently launched the “Purple Book,” more properly known as the “Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations” [38]. It is designed to be referred-to by the nickname “Purple Book” in the same way as they reference the “Orange Book,” which lists approved drug products with therapeutic equivalence evaluations for small molecule drugs. There are separate lists for products regulated by Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), and these will be updated regularly.

Naming of monoclonal antibodies and biosimilars

One of the important aspects of any drug is the name by which patients, providers, and all those involved in the health care system will call the entity. All monoclonal antibody names end with the stem *-mab*. A different preceding word is used depending on structure and function. These are officially called *substems* and sometimes as *infixes*. The substem preceding the stem denotes the animal from which the antibody is obtained. The first monoclonal antibodies were produced in mice (substem *-o-*, yielding the ending *-omab*). These non-human antibodies are recognized as foreign by the human immune system and may be rapidly cleared from the body, provoke an allergic reaction, or both. To avoid this, parts of the antibody is replaced with human amino acid sequences, or pure human antibodies can be engineered. If the constant region is replaced with the human form, the antibody is termed *chimeric* and the substem used is *-xi-* (as in *Infliximab*). Part of the variable regions may also be substituted; in which case, it is called *humanized* and “*-zu-*” is used (As in *trastuzumab*).

An indication about the target of the antibody, such as tumors, organ systems (e.g. circulatory), or infectious agents such as bacteria or virus is also inserted in its name. In the naming scheme as originally developed, these substems mostly consist of a consonant, a vowel, then another consonant. The final letter may be dropped if the resulting name would be difficult to pronounce otherwise. Examples include *-ci(r)* - for the circulatory system, *-li (m)* - for the immune system (lim stands for lymphocyte) and *-ne(r)* - for the nervous system. The final letter is usually omitted if the following source substem begins with a consonant (such as *-zu-* or *-xi*). Combination of target and source substems results in endings like *-limumab* (immune system, human) or *-ciximab* (circulatory system, chimeric).

New and shorter target substems were adopted in 2009 [39]. They generally consist of a consonant, plus a vowel which is omitted if the source substem begins with a vowel. For example,

human antibodies targeting the immune system receive names ending in *-lumab* instead of the old *-limumab*. Some endings like *-ciximab* remain unchanged.

A prefix is used to distinguish between two antibodies with the same source and target [40]. Even antibodies targeting exactly the same structure are differently prefixed, such as the *adalimumab* and *golimumab*, both of which are TNF inhibitors but differ in their chemical structure.

A second word following the name of the antibody indicates that another substance is attached, which is done for several reasons. An antibody can be PEGylated (attached to molecules of polyethylene glycol) to slow down its degradation by enzymes and to decrease its immunogenicity; this is shown by the word *pegol* as in *alacizumab pegol*. A cytotoxic agent can be linked to an anti-tumor antibody for drug targeting purposes. If the drug contains a radioisotope, the name of the isotope precedes the name of the antibody. Consequently, indium (^{111}In) *capromab pendetide* is the name for the above example including indium-111 [41].

In January 2017, the FDA finalized long-awaited guidance (initially published in August 2015) for the nonproprietary names of biologics and biosimilars [41]. The guidance recommends that the name should consist of a core name of the product followed by a unique suffix of four lower case letters. For example, *filgrastim-sndz*, *Infliximab-dyyb*. This naming convention is applicable to biological products previously licensed and newly licensed under the PHS Act. The original product and biosimilar will have the same core name but different suffixes. The suffix should be devoid of any specific meaning. This has been contested later by pointing out that the suffix *-sndz* here actually denote Sandoz. FDA is also considering whether the nonproprietary name for an interchangeable product should include a unique suffix, or should share the same suffix as its reference product.

Filgrastim

Filgrastim-sndz (Zarxio; Sandoz/Novartis) was the first biosimilar (to filgrastim [Neupogen]) approved in the US in March 2015 [42]. It was approved in Europe in 2009. Filgrastim-sndz has the same indications as filgrastim, including to decrease the risk of infection and febrile neutropenia for patients receiving chemotherapy and to reduce the duration of neutropenia, among others [43].

Infliximab

Infliximab-dyyb (Inflectra; Pfizer/Celltrion), a biosimilar to infliximab (Remicade; Janssen), was approved on April 5, 2016. The mAb infliximab reference product was approved by the FDA in 1999. Besides ulcerative colitis and Crohn's disease, infliximab is also used to treat rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, and ankylosing spondylitis. Infliximab is a chimeric mAb that works against tumor necrosis factor alpha (TNF- α) and is used to treat autoimmune diseases. It is used as an intravenous infusion, typically at 6-8 week intervals [44]. Infliximab is an artificial antibody. It was originally developed in mice as a murine antibody. Because humans have immune reactions to mouse proteins, the mouse common domains were replaced with similar human antibody domains. Because infliximab is a com-

ination of mouse and human antibody amino acid sequences, it is called a “chimeric monoclonal antibody.” The FDA approved infliximab-dyyb based on reviews of evidence that ranged from structural and functional characterization to human pharmacokinetic data.

To date, infliximab biosimilars have been approved in the EU (2013), Japan (2014), and USA (2016). In June 2013, two biosimilar versions of infliximab (Inflectra and Remsima) were submitted for approval in Europe by Hospira and Celltrion Healthcare, respectively [45]. Celltrion obtained marketing authorization approval (MAA) from 27 EU countries and 3 EEA (European Economic Area) countries by Sept 2013. In Japan, Celltrion received marketing authorization for Remsima in July 2014. In India, Ranbaxy and Epirus Biopharmaceuticals obtained approval to produce biosimilar infliximab under the brand name “Infimab” [46].

Other mAbs targeting TNF- α include adalimumab, golimumab and certolizumab pegol. Etanercept also binds and inhibits TNF- α , but is structurally different in that it is a fusion protein between the TNF receptor and an antibody constant region [47]. The anti-TNF antibodies adalimumab and infliximab have the capability of lysing cells involved in the inflammatory process, whereas the receptor fusion protein apparently lacks this capability. These differences may account for the differential actions of these drugs in both efficacy and side effects.

Etanercept

Etanercept-szszs (Erelzi; Sandoz) was approved by the FDA on August 30, 2016 for the treatment of multiple inflammatory diseases, including moderate to severe rheumatoid arthritis and moderate to severe plaque psoriasis, among others. Erelzi, a subcutaneous TNF- α inhibitor, was approved as biosimilar to Enbrel (etanercept; Amgen Inc.), which was licensed in 1998. Erelzi has not been approved as an interchangeable product. The European medicine agency approved Benepali (Samsung Bioepis), the first biosimilar of Enbrel in Europe on November 19, 2015 [47,48].

Etanercept is a large molecule (150,000 Da) fusion protein produced by recombinant DNA in a Chinese hamster ovary (CHO)-mammalian cell expression system. It contains 934 amino acids. The fusion is between the TNF receptor and the constant end of the IgG1 antibody. First, the developers isolated the DNA sequence that encodes the human gene for soluble TNF receptor 2, which is a receptor that binds to TNF- α . Second, they isolated the DNA sequence that encodes the human gene for the Fc end of immunoglobulin G1 (IgG1). Third, they linked the DNA for TNF receptor 2 to the DNA for IgG1 Fc. Finally, they expressed the linked DNA to produce a protein that links the protein for TNF receptor 2 to the protein for IgG1 Fc. The prototypic fusion protein was first synthesized and shown to be highly active and unusually stable.

Etanercept mimics the inhibitory effects of naturally occurring soluble TNF receptors with a significant difference. Because etanercept is a fusion protein rather than a simple TNF receptor, it has a greatly extended half-life in the bloodstream and therefore a more profound and long-lasting biologic effect than a

naturally occurring soluble TNF receptor [49]. Enbrel has traditionally been more expensive in the US than in other countries. As of 2013, the average monthly costs in surveyed nations ranged from \$1,017 in Switzerland to \$1,646 in Canada, compared to an average monthly cost of \$2,225 per month in the US [50].

Adalimumab

Adalimumab-atto (Amjevita; Amgen, Inc), a biosimilar version of adalimumab (Humira; AbbVie, Inc.), was approved by the FDA on September 23, 2016 [51]. Humira was at the top of the list of highest selling drug in 2014 but moved to second position in 2015 (about \$15 billion) and costs approximately \$3,100 per month in the US [52].

Adalimumab-atto is approved for the same conditions as adalimumab: moderately to severe active rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, moderate to severe Crohn’s disease, moderate to severe ulcerative colitis, and moderate to severe plaque psoriasis. Adalimumab-atto is not an interchangeable product and therefore cannot be substituted for Humira by a pharmacist. While FDA-approved, adalimumab-atto has not been launched for distribution by Amgen yet, due to ongoing litigation with AbbVie related to patent protections on Humira [53].

Like most biologic products discussed in this article, adalimumab is a large glycoprotein and consists of a heterogeneous mixture of structural isoforms [54]. Like Humira, the labeling for Amjevita contains a boxed warning to health care professional and patients about an increased risk of serious infections. The warning also notes that lymphoma and other malignancies have been reported in children and adolescent patients treated with tumor necrosis factor blockers [55].

Adalimumab quality assurance

It is a concern whether the quality of the biological product can be reproduced by manufacture in different places, from different sources, and with varying bioprocessing techniques. To gain information about this, a study was carried out to determine the structural consistency of Humira from different sources [56]. This report also included the criteria necessary to establish and maintain biosimilarity. First, it is necessary to assess surface charge of the drug substance, which is a feature sensitive to changes in manufacturing process. Second, the glycosylation pattern leads to different isoforms and is considered a unique signature of mAbs. It influences their function and is important for determining comparability. Differences in the glycosylation pattern and C-terminal lysines can affect the tertiary and quaternary structure of a therapeutic protein. Normal phase HPLC can be used to determine the oligosaccharides on conserved N-linked glycosylation sites [57]. In addition to glycosylation, enzymatic hydrolysis of the C-terminal lysines contributes to heterogeneity of mAb [58]. Third, TNF- α binding can be studied by surface plasmon resonance measurements. Finally, according to Venema et al, it is necessary to analyze clinical efficacy data over time using meta-analysis techniques [56].

Biosimilars in the pipeline

BioProcess International estimated in 2013 that there were 514 biosimilar and 402 biobetter candidates in development, for a total of 916 products. The Pharmaceutical Research and Manufacturers Association estimate 907 products in the clinical development pipeline [59]. For example, Humira (adalimumab) has 13 biosimilars and 8 biobetters, Enbrel (Etanercept) has 21 biosimilars and 8 biobetters, Herceptin (trastuzumab) has 24 biosimilars and 12 biobetters, Avastin (bevacizumab) has 14 biosimilars and 9 biobetters, and tumor necrosis factor inhibitors have 44 biosimilars and 19 biobetters [59]. About 232 biosimilars are in the preclinical stages. Mylan and Biocon have applied for FDA approval (November 2016) for biosimilars of Herceptin to treat HER-2 positive breast and gastric cancers. Mylan and Biocon's proposed biosimilar trastuzumab is also under review by the European Medicines Agency. Other companies are also developing biosimilars of Herceptin. South Korea's Celltrion has already submitted an application for approval in Europe. Allergan and Amgen have obtained positive phase 3 data for their version of the drug [60].

Sandoz is planning multiple additional biosimilar application submissions, including versions of Amgen's Epogen (epoetin alfa), AbbVie's Humira (adalimumab), and Roche's Rituxan (rituximab). Boehringer Ingelheim announced that BI695501, its adalimumab biosimilar candidate to Humira, has been accepted for regulatory review by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) [61].

Amgen has also made regulatory submissions for biosimilar versions of three major products: Avastin (bevacizumab), Herceptin (trastuzumab) and Erbitux (cetuximab). Pfizer's clinical stage pipeline biosimilars include five monoclonal antibodies ranging from phase 1 through phase 3 clinical development which span autoimmune diseases and oncology.

Pharmacoeconomics of biosimilars

Affordability of the biologic drugs is a concern for patients, insurance companies, and law makers. It is estimated that an average biologic drug cost 20 times more than a small molecule drug, and some of the best-selling drugs such as Herceptin and Humira may cost anywhere between \$37,000-\$200,000 per year to patients [62,15].

The drug Remicade (Infliximab) and its biosimilars are available in several countries: Inflectra (EU and US), Remsima (71 countries around the world, not approved in US), Renflexis (Korea) and Infimab (India). Like all of the TNF inhibitors, infliximab is an expensive medication, costing about US \$900 for a 100 mg dose. Infliximab is supplied as a sterile, white, lyophilized (freeze-dried) powder. It must be reconstituted and administered by a health care professional, usually in a hospital or office setting. For this reason, it is usually covered under major medical insurance rather than prescription drug coverage.

Infliximab is available from the National Health Service in the UK for Crohn's disease and ulcerative colitis treatment. It is available through the Pharmaceutical Benefits Scheme in Australia for Crohn's disease treatment, provided the patient has not responded to conventional treatment and is suffering from a severe

case of the condition. Infliximab is available in the Republic of Ireland through the Health Service Executive's Medical Card and Drug Payment Scheme. The Cost of infliximab is reduced by 30-40% in most European countries and is covered by their insurance. The competition is expected not only to drive down prices, but also to increase access to drugs for patients.

Compared to an average of 3 years and \$1-4 million between development and approval of a drug in the generic market, it takes 7-8 years to develop a biosimilar at a cost of between \$100-250 million [63, 64]. In general, generic small molecule drugs cut the cost of brand name drugs by 60-80%. For biosimilars, however, expectations are not as high. A 20-30% reduction over the reference product may be more typical, perhaps even 15% [65]. Some of the bestselling biologic drugs may cost from \$37,000 to \$200,000 per year to the patient. Zarxio (biosimilar to Neupogen) saves the patient about 15%, with prices set at \$275 for a 300mg syringe and \$439 for a 480mg syringe as compared to Neupogen at \$324 and \$516 respectively [66]. Infliximab, like other TNF- α inhibitors, is expensive, costing about \$900 for a 100mg dose. Global sales for infliximab were \$10.1 billion in 2014 [67]. Neupogen, a drug with more than two decades on the market, posted US sales of \$963 million in 2013. The third biosimilar approved by FDA this year, had \$9.5 billion in global sales last year.

Celltrion has invested about \$200 million in Remsima, biosimilar to Remicade. Avastin's (Bevacizumab) global sales in 2014 were \$8.1 billion, and for Herceptin (trastuzumab) global sales were \$6.6 billion in 2014 [67]. The global biosimilars market was \$1.3 billion in 2013 and is expected to reach \$35 billion by 2020, driven by the patent expiration of additional ten blockbuster biologic drugs [53].

Conclusions

Biosimilars are alternative treatment options for the more expensive reference product. These potentially life-saving and lower-cost versions are more affordable and accessible for patients with a wide variety of diseases, including cancer. However, it is a concern for prescribers and users whether the quality of the complex biological product can be reproduced by manufacture in different locations, from different sources, and varying bioprocessing conditions. Both the US and European regulatory pathways depend on the ability to demonstrate biosimilarity, involving rigorous comparison against batches of originator product and appropriate comparative safety and efficacy tests. Because of the difficulty in producing an exact copy of the innovator's product, the FDA permits "allowable differences." Consistency of structural attributes of the biosimilars, which can be measured by modern analytical techniques, indicate consistency in clinical performance.

The art of biosimilar development consists of matching critical attributes that are necessary for function of reference product with that of the biosimilar. One complicating factor is understanding which attributes must be matched. It is also necessary to establish by appropriate methods that there is no negative clinical impact when switching between originator and biosimilar therapies.

Even though there are only four biosimilars approved by FDA so far, all indications are that many more are likely to be approved soon.

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