Drugs (2017) 77:985–997
DOI 10.1007/s40265-017-0743-z

REVIEW ARTICLE

Current Status of Biosimilars in Oncology

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Published online: 5 May 2017
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Abstract Four medicinal cancer biological blockbusters will end their patent lifespan by 2020. It is estimated that the total market for cancer biologicals will reach approximately US$68 billion at that time. Approximately 20 biosimilars have entered the European market since the launch of the original approval guidelines in 2005, and four biosimilars have been approved in the USA since 2015. Data from European countries with the highest market entrance of biosimilars suggest that the incorporation of biosimilars into healthcare systems worldwide may result in a 30–45% cost savings. Initial levels of apprehension expressed by healthcare providers regarding the safety and efficacy of integrating biosimilars into the treatment of cancer patients have gradually decreased through active educational programs. The trust generated by regulatory agencies and drug manufacturers will ultimately make the adoption of biosimilars by healthcare providers and patients a smooth process. Future efforts to improve on the global acceptance and safety of biosimilars must include standardization of naming, regulatory requirements, and pharmacovigilance programs worldwide. High expectations are being placed on the cost savings, safety, and efficacy of these products. The entry costs for biosimilars and the pricing reaction of their originator products will determine the true savings by troubled health systems in dire need of cost cuts. This article discusses basic principles of biosimilars in hematology and oncology, the current status of their clinical development, and trends of acceptance by healthcare providers, and provides insight into potential future challenges.

Key Points

Biosimilars are biological compounds developed to fill treatment opportunities generated by patent expiration of approved reference medications.

Unlike generic medicinals, biologicals are very complex therapeutic agents.

Compared to the reference products, biosimilars are expected to decrease treatment costs by approximately 30%.

The approval process for biosimilars is different from that of the originator compounds.

General concerns regarding the safety and efficacy of biosimilars have decreased over time as the medical community and patient advocacy groups become more familiar with the characteristics and approval pathways for biosimilars.

1 Introduction

Traditional *chemical drugs* differ greatly from *biological agents*. There are major differences between both groups of compounds: while conventional medicinals are small chemically based *structures*, biologicals are large and more complex protein-based structures. The *characterization* of these compounds is also substantially different. While

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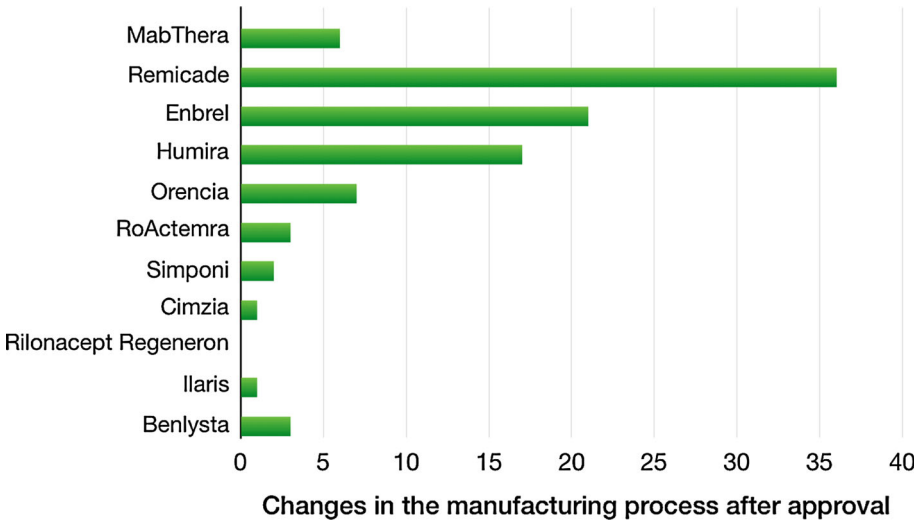

Fig. 1 Number of changes in the manufacturing process of selected European Biologicals after approval Reproduced with permission from: Schneider [3]

biologicals are difficult to characterize, chemicals have much simpler structures. Their *degradation* is also dissimilar; chemical drugs have simple and well-established mechanisms, whereas the degradation of biologicals is fairly complex. Perhaps one of the greatest differences among these groups of agents is their *manufacturing* process. Chemical agents are the result of predictable and controlled reactions, while the manufacturing of biologicals requires the use of living sources and far more expensive and sophisticated quality control [1]. Biologicals tend to be heat-sensitive and susceptible to microbial contamination, while chemical drugs are far more resistant [2]. Finally, due to its living organism-based development process, biologicals are quite heterogeneous and it is not uncommon for biologicals to undergo several changes in their manufacturing process throughout their lifetime (Fig. 1) [3].

Drug patents are granted by the patent and trademark office and expire 20 years after initial filing. The term *exclusivity* refers to the marketing rights granted by the US Food and Drug Administration (FDA) upon drug approval and may run in parallel with the patent. Exclusivity rights were developed to balance new drug innovation and generic drug competition. However, the exclusivity of a product may vary from days to years [4].

In 2014, American pharmacists dispensed 4.3 billion prescriptions. Of these, almost 3.8 billion (88%) were generic formulations. While generic drugs comprised only 28% of the total medication costs, Americans saved US$254 billion using generic drugs [5]. Furthermore, the cumulative savings from using generics was US$1.68 trillion between 2005 and 2014. Four of the top ten biological blockbusters[1] used worldwide are either therapeutic or supportive cancercare agents. The patents of these four agents will expire by the year 2020, opening market opportunities for similar agents to compete with their reference products. It is estimated that by then, the total market for cancer biologicals will reach approximately US$68 billion [6]. In addition to stimulating the market of biological drugs, developing biosimilars is less expensive—as a result of abbreviated approval pathways and highly similar manufacturing processes—and although far from their generic counterparts, this trend is expected to result in substantial healthcare savings around the globe. This article reviews basic concepts on biosimilars, outlines the importance and implications of their development and implementation, analyzes the regulatory pathways in the USA and the European Union, and provides an update on the status of their acceptance by US clinicians.

2 Key Terms to Best Understand Biosimilars

According to the World Health Organization (WHO), a biosimilar is "A biotherapeutic product, which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product" [7]. According to the FDA, a biosimilar is "a biological product submitted in a 351(k) application that has been shown to be highly similar to the reference product *notwithstanding minor differences* [author's emphasis] in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product (see section 351(i)(2) of the PHS Act)" [8].

2.1 Reference Product

A *reference product* is a single biological product registered under section 351(a) of the Public Health Service Act

[1] Blockbusters are drugs that generate at least US$1 billion for the company that develops them.

(PHS Act) of the USA [9]. Under section 351(k)(7), the licensure of an application for a biosimilar may not be effective by the FDA until 12 years after the reference product was first licensed. Additionally, a biosimilar [351(k)] application may not be submitted to review until 4 years after the time of first licensure of the reference product. This time is known as the reference product *exclusivity period*.

2.2 Variability

Variability refers to non-clinically meaningful differences in the production of a biological agent. These differences must not affect the safety, purity, or efficacy of the biotherapeutic. It is also important to note that batch-to-batch variability is inherent to all biologicals, both for reference products and biosimilars.

2.3 Extrapolation of Indications

Biosimilars may receive FDA approval for one or more of the indications for which the US reference product has been approved based on data demonstrating similarity in one of the indications for which the reference product was approved. While confusing to some, this mechanism avoids the conduct of large clinical trials that would otherwise hamper the cost savings associated with developing biosimilars. However, sufficient scientific data are required to support approval across indications. Importantly, extrapolation may also take place across conditions.

2.4 Totality-of-the-Evidence Approach

In demonstrating biosimilarity, the FDA will evaluate the entirety of the data submitted in the application (structural and functional characterization, non-clinical evaluation, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data, and comparative clinical data) [10]. This approach has been selected to improve the efficiency of the approval process.

2.5 Interchangeability

The concept of interchangeability is exclusive to the FDA. It means that a product (1) is biosimilar to a reference product; (2) is expected to produce the same clinical outcome as its reference product in any given patient; (3) if administered more than once to an individual, has a risk in terms of safety or decreased efficacy of alternating or switching the use of the biosimilar and its reference product that is not greater than using the reference product alone without the alternation or switch. Importantly, according to the FDA the ultimate purpose of this regulatory figure is that "An interchangeable biological product may be substituted for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product" [8].

2.6 Fingerprint-Like Analysis

Extensive functional and structural characterization of biosimilars must be conducted in a stepwise fashion to demonstrate high similarity between the biosimilar and the reference product. The FDA believes that using a fingerprint-like analysis algorithm is an efficient approach to demonstrate a large number of product properties with high sensitivity to guide further studies [11].

2.7 Pharmacovigilance

According to the WHO, pharmacovigilance is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" [12]. The adherence to a strict pharmacovigilance program is critical to closely follow the post-marketing safety of biosimilars.

3 Biologicals in Oncology

Traditional cytotoxic chemotherapy was developed to kill cancer cells by affecting different stages of the cell cycle, critical DNA structures, or impairing DNA repair mechanisms. Historically, these drugs may cure most localized tumors and may also induce major responses in patients with regionally or systemically advanced disease. In other patients, cytotoxics may effectively decrease tumor burden, alleviate symptoms, and positively impact their survival [13]. In contrast, biological agents are compounds developed against critical components of the cancer cell or involved signaling pathways. In addition to increasing cancer survival, they are for the most part safer products, and may be administered alone or in combination with chemotherapy. Biologic agents have molecular weights ranging between 4000 Da for non-glycosylated proteins and 140,000 Da for monoclonal antibodies, whereas small molecules usually range between 150 and 800 Da [14]. According to the FDA, "Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins" [2]. Recombinant biologic agents are peptides or proteins manufactured through the manipulation of gene expression in an

organism so it produces large quantities of a particular recombinant gene product. The process can take place in 'expression systems', which typically include cell-based systems and cell-free systems.

The development of biological agents to treat cancer became possible in the 1980s. Interferon-α-2b (INTRON A™, Schering Corporation, Kenilworth, NJ, USA) received its first FDA label approval in June 1986 and currently holds seven different labels, including patients with hairy cell leukemia, follicular lymphoma, high-risk melanoma, and AIDS-related Kaposi's sarcoma [15]. Epoetin-α (Epoetin/Procrit™, Amgen, Inc., Thousand Oaks, CA, USA) received its approval in June 1989. The drug currently holds labels for patients with anemia of chronic disease, anemia of concomitant chemotherapy, anemia associated with zidovudine in HIV-infected patients, and patients undergoing elective, non-cardiac, non-vascular surgery [16]. *Filgrastim* (Neupogen™, Amgen, Inc.) received FDA approval in February 1991 for cancer patients receiving myelosuppressive chemotherapy, and currently holds four different labels, including patients with acute myeloid leukemia receiving induction or consolidation chemotherapy, cancer patients receiving a bone marrow transplant, and bone marrow stimulation to collect peripheral blood progenitor cells prior to autologous stem cell transplant in selected hematological malignancies [16]. Subsequently approved biologicals include interleukin-2 (May 1992; Proleukin™, Prometheus Laboratories Inc., San Diego, CA, USA; previously owned by Chiron Corporation, Emeryville, CA, USA), and several monoclonal antibodies and vaccines including rituximab (November 1997), *trastuzumab* (September 1998), peg-filgrastim (January 2002), *cetuximab* (February 2004), bevacizumab (February 2004), *panitumumab* (February 2006), and sipuleucel-T (April 2010). As expected, the patents for these products have expired or are about to expire, and biosimilars are under development.

The European Medicines Agency (EMA) developed biosimilar approval guidelines in October 2005 [17]; Omnitrope™, a recombinant growth factor hormone, became the first EMA-approved biosimilar in April 2006. Since the approval of Omnitrope™, nearly 20 agents have entered the European market, and approximately 30 more are expected to do so by 2020. Furthermore, it is estimated that the entry of biosimilars in Europe has resulted in a 44% increase in patient access to these medications in countries where biosimilars have reached greatest penetration [18]. The FDA has approved four biosimilars since 2015 (Table 1). Similar to the EMA and FDA, other regulatory entities around the world are in the process of adopting or implementing guidelines for the approval of biosimilars.

4 Regulatory Aspects of Biosimilars

The US's Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) was developed with two critical goals in mind: (1) Congress wanted to ensure that brand-name (innovators) drug manufacturers would have patent protection and a period of exclusivity enabling recovery of their upfront investments in the development of new drugs; and (2) Congress also wanted to ensure that, once the innovator's patent protection and exclusivity period expire, consumers would benefit from the rapid availability of lower-priced generic versions of innovator drugs [19]. Since the Hatch-Waxman Act was enacted in 1984, it has governed the approval process for generic drugs in the USA. On 23 March 2010, the US Congress passed the Biologics Price Competition and Innovation Act (BPCI Act) of 2009 as part of the Affordable Care Act. Similar to the Drug Price Competition and Patent Term Restoration Act, the BPCI Act attempts for biologics to mirror the broad availability and cost savings of their chemical counterparts. Additionally, the FDA has committed to saving time and resources while avoiding unnecessary duplication of human or animal testing for the development of biosimilars. Fifty-nine biosimilar products to 18 different reference products were enrolled in the FDA's Biosimilar Product Development (BPD) Program by January of 2016. The BPD Program is part of the Biosimilars User Fee Act (BsUFA) to provide a mechanism and structure for the collection of development-phase user fees to support the FDA's biosimilar review program activities. The number of sponsors registered in the BPD Program is not fully reflective of the number of industry programs underway, as sponsors may be in early stages of interactions with the FDA and not yet enrolled in the program [20].

5 Naming of Biological Products

From a safety standpoint, an international biosimilar nomenclature is much desired and needed. However, such consensus is far from reached. In 1950, the WHO developed the International Nonproprietary Name (INN) by a World Health Assembly Resolution (WHA3.11). The INN came into operation in 1953 and identifies a pharmaceutical substance or active pharmaceutical ingredient by a unique name that is globally recognized and is public property. This name is also known as the *generic name*. The cumulative list of INNs includes approximately 7000 names and continues to grow at a rate of 120–150 INNs per year [21, 22]. INN experts have adopted unique nomenclature for all medicinals, including biologics. The main

Table 1 Biosimilars approved by the European Medicines Agency and US Food and Drug Administration until November 2016 Adapted from Siegel and Fischer [25] and Generics and Biosimilars Initiative online [39])

Trade name	Company	Active substance	Reference biological	Year of approval
EMA				
Erythropoietin-stimulating agents				
Abseamed	Medice	Epoetin-α	Eprex/Erypro	2007
Binocrit	Sandoz	Epoetin-α	Eprex/Erypro	2007
Epoetin-α Hexal	Hexal	Epoetin-α	Eprex/Erypro	2007
Retacrit	Hospira	Epoetin-ζ	Eprex/Erypro	2007
Silapo	Stada	Epoetin-ζ	Eprex/Erypro	2007
Growth colony-stimulating factors				
Accofil	Accord	Filgrastim	Neupogen	2014
Biograstim	AbZ-Pharma	Filgrastim	Neupogen	2008
Filgrastim Hexal	Hexal	Filgrastim	Neupogen	2009
Grastofil	Apotex	Filgrastim	Neupogen	2013
Nivestim	Hospira	Filgrastim	Neupogen	2010
Ratiograstim	Ratiopharm	Filgrastim	Neupogen	2008
Tevagrastim	Teva	Filgrastim	Neupogen	2008
Zarzio	Sandoz	Filgrastim	Neupogen	2009
Parathyroid hormones				
Terrosa	Gedeon Richter	Teriparatide	Parathyroid hormone	2016 (good opinion 10 November 2016)
Movymia	STADA Arzneimittel	Teriparatide	Parathyroid hormone	2016 (good opinion 10 November 2016)
Follitropins				
Bemfola	Finox	Follitropin-α	GONAL-f	2014
Ovaleap	Teva	Follitropin-α	GONAL-f	2013
Growth hormones				
Omnitrope	Sandoz	Somatropin	Genotropin	2006
Insulins				
Lusunda	Merck (MSD)	Insulin glargine	Lantus	Positive review 10 November 2016
Abasaglar	Eli Lilly	Insulin glargine	Lantus	2014
Monoclonal antibodies/fusion proteins				
Inflectra	Hospira	Infliximab	Remicade	2013
Remsima	Celltrion	Infliximab	Remicade	2013
Benepali	Samsung Bioepis	Etanercept	Enbrel	2016
Flixabi	Samsung Bioepis	Infliximab	Remicade	2016
US FDA				
Growth colony-stimulating factors				
Zarxio	Sandoz	Filgrastim	Neupogen	2015
Monoclonal antibodies/fusion proteins				
Inflectra	Celltrion & Pfizer	Infliximab	Remicade	2016
Erelzi	Sandoz	Etanercept	Enbrel	2016
Amjevita	Amgen	Adalimumab	Humira	2016

EMA European Medicines Agency, *FDA* Food and Drug Administration

concern is that according to the WHO, more than 40% of applications to the INN program correspond to biologicals, and this number is increasing. Therefore, their proposal is to use the INN and a Biological Qualifier (BQ). The proposed BQ would consist of four letters (excluding vowels). Such a suffix would allow 160,000 combinations and provide a large number of potential names for future biosimilars [23]. Below are some examples of the

nomenclature assigned to oncology biologicals under review by FDA and EMA [21].

- *Growth factors:* the general stem *–stim* was selected for all colony-stimulating factors; *–distim* was assigned to a combination of two different colony-stimulating factors; granulocyte–colony-stimulating factor (G-CSF) substances were given the stem *–grastim* and the term *–gramostim* was assigned to granulocyte macrophage–colony-stimulating factor (GM-CSF) substances.
- *Erythropoietins:* The term epoetin followed by a Greek letter was designated to differentiate between compounds of the same amino acid sequence as human erythropoietin, which may have different glycosylation patterns. If a different amino acid sequence is reported, the stem *–poietin* is used with a different and random prefix.
- *Monoclonal antibodies*. The general stem for monoclonal antibodies is *–mab*. If human, the antibody will use the sub-stem *-u-*; if mouse originated *-o-*, or *-zu-* for humanized products. Chimeric antibodies use the sub-stem *-xi-*.

The FDA believes that shared non-proprietary names are not appropriate for all biological products. In order to clearly differentiate biologicals, maximize their safe use, and facilitate their pharmacovigilance, the FDA issued naming guidelines for biologicals. Under current FDA guidelines, the *proper name* for a biological must include a *core name* and a *designated suffix*. The core name is the component shared among all related biological products as part of the proper name. Two examples of a core name are filgrastim and epoetin-α. The proper name for all biological products will include a designated suffix composed of four lowercase letters attached to the core name with a hyphen. For originator biological compounds, the FDA intends to use the core name adopted by the United States Adopted Names (USAN) Council for the drug substance. "If the biological product is a related, biosimilar, or interchangeable product, the *core name* will be the name of the drug substance contained in the relevant previously licensed product. A designated suffix composed of four lower case letters will be added to the *core name* of each product and will be attached with a hyphen" [8, p. 7]. The FDA requests that the suffix be (1) four lowercase letters; (2) unique; and (3) devoid of meaning. It also requests that it should not (1) be promotional—by making representations of safety or efficacy; (2) include abbreviations commonly used in practice such that it may mislead to be interpreted as another element of the prescription or order; (3) contain or suggest any drug substance name or core name designated by the USAN Council; (4) look similar to or be mistaken for the name of a currently marketed product; or (5) be too similar to any other product's suffix designation [8]. According to the FDA, "the proper name of a biological product must reflect certain scientific characteristics of the product, such as the chemical structure and its pharmacological properties". This name is different from a *proprietary name*, which generally is trademarked and registered for private use. For biological products licensed under the PHS Act, the FDA designates the *proper name* in the license for use upon each package of the biological product (see section 351(a)(1)(B)(i) of the PHS Act and § 600.3(k)). Furthermore, the proper name should help healthcare providers to identify the product's active drug and distinguish biologics from one another. The FDA is also studying a uniquely designated suffix for *interchangeable products*, or alternatively, to allow those compounds to share *proper name and suffix* with their reference product [8]. The FDA is still open to receiving and considering feedback regarding potential alternatives to the naming convention established for interchangeable products. A recent electronic report informs of a letter issued by the FDA in response to a 70-group request sent in May 2016 asking the agency to consider the use of meaningful suffixes for approved biosimilars—similar to that used for Zarxio™ (filgrastim-sndz; Sandoz, Princeton, NJ, USA) but different from that assigned for Inflectra™ (infliximab-dyyb; Celltrion, Yeonsu-gu, Incheon city, Republic of Korea & Pfizer, New York, NY, USA), which used a random suffix that does not reflect the name of the manufacturing company [24]. The FDA also expects "to receive a total of 40 annual requests for the proposed proper name for biologics, and six requests annually for the proposed proper name for biosimilars and interchangeable products" [24]. However, officers from the European Biosimilars Group (EBG) and other authorities feel that the addition of a suffix to a biosimilar core name may add potential error margin for pharmacy and healthcare providers. Other regulatory agencies have adopted their own biosimilar nomenclature. While in Japan, the code 'BS' (biosimilar) is added to the core name (i.e., epoetin-α BS), South Korea has allowed the use of proprietary names as identifiers. It assigned the name 'Herzuma' to Celltrion's biosimilar of Roche's trastuzumab. The EMA authorities recommend the applicant or Marketing Authorization Holder (MAH) should consult the EMA's Name Review Group (NRG), understanding that the INN designation is the responsibility of the WHO. The applicant or MAH must consider the WHO INN guidelines to decide whether the proposed biosimilar may use the same INN as its reference product or if a new INN is to be requested from the WHO. In Europe, biosimilars are generally known by their trade names, which are different from those of the brand-name

reference drug, but the non-proprietary names of European biosimilars are identical to those of their originator [25].

6 Biosimilars in Clinical Trials

The development program for biosimilars is aimed at establishing biosimilarity between a biosimilar and its reference product. Clinical trials evaluating biosimilars in oncology are intended to confirm the initial similarity established during initial pharmacokinetic and pharmacodynamic evaluations. Safety is an important aspect to determine the comparability of these agents [10, 26].

A search for biosimilar clinical trials was conducted in the US National Institutes of Health clinical trials website (http://www.clinicaltrials.gov). On 6 November 2016, the site reported 40,099 registered clinical trials. Of those, 56% were non-US only, 39% US only, and 5% both non-US and US originated. Using the terms "biosimilar AND oncology ($n = 136$)", "biosimilar AND cancer ($n = 136$)", "biosimilars AND cancer ($n = 5$)", "biosimilar AND anemia ($n = 12$)", the search engine found 136 studies (Table 2). However, a detailed review of each trial retrieved in the search found only 30 clinical trials meeting criteria for biosimilars in hematology and oncology. Multiple other search terms were used and the number of eligible trials was not increased. An important limitation of this search is the fact that biosimilar trials are not necessarily listed under the search term 'biosimilar' but rather the pre-approval product name. Of the 30 trials encountered in this search, the distribution by medical conditions included the following: anemia = 11; breast cancer = 7; neutropenia = 6; lymphoma = 4; lung cancer = 2; and colorectal cancer = 1. This suggests that there is still a majority of growth factor biosimilars under development. Other agents included biosimilars to trastuzumab, bevacizumab, and rituximab originators. These monoclonal antibodies with therapeutic intent will be the second wave of biosimilars in the US and Europe.

6.1 Trastuzumab

Trastuzumab (Herceptin®; Genentech, South San Francisco, CA, USA) is a recombinant DNA-derived humanized monoclonal antibody with high affinity for the extracellular domain of the human epidermal growth factor receptor 2 (HER2)/neu protein. Trastuzumab has demonstrated tumor cell growth suppression in vitro and in vivo. Trastuzumab received FDA approval for the treatment of advanced HER2/neu overexpressing breast cancer, gastric and gastro-esophageal carcinoma, and in the adjuvant setting of HER2/neu overexpressing breast cancer [27]. Trastuzumab had sales of US$6.6 billion in 2015. The patents on Herceptin® expired in Europe in July 2014 and will expire in the US in June 2019. Several trastuzumab biosimilars are undergoing development. Samsung Bioepis pre-registered trastuzumab biosimilar SB3 for breast and gastric cancer in Europe and obtained an EMA review acceptance letter on 3 October 2016. Celltrion submitted an approval request to the EMA for trastuzumab biosimilar Herzuma™ (CT-P6) on 27 October 2016 [28]. Mylan Inc. sponsored a randomized phase III trial presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in June 2016. The HERiTAge study randomized 500 women with metastatic, HER2 (+) positive breast cancer to receive front-line taxane-based chemotherapy with either trastuzumab or MYL-1401O (the trastuzumab biosimilar). MYL-1401O and trastuzumab demonstrated equivalent efficacy, safety, and immunogenicity. The objective response rates at 24 weeks were 69.6% with MYL-1401O and 64% with trastuzumab. The immunogenicity and safety were comparable between both treatment groups. The incidence of serious adverse events was 36% for trastuzumab and 38% for MYL-1401O. The most common serious adverse effect was neutropenia, and there was no difference in cardiac function between the two arms. Four treatment-related deaths were reported in each group (ClinicalTrials.gov identifier NCT02472964) [29]. Pfizer is developing trastuzumab biosimilar PF-05280014. A three-arm study in healthy volunteers was presented by Yin et al. [30] at the 2013 annual ASCO meeting demonstrating pharmacokinetic and safety similarity between PF-05280014, trastuzumab-US, and trastuzumab-EU (NCT01603264) [30]. A clinical trial comparing PF-05280014 with Herceptin® (trastuzumab-EU) plus paclitaxel in front-line treatment of patients with metastatic HER2 (+) breast carcinoma (REFLECTIONS B327-02) is ongoing (NCT01989676). In July 2016, Amgen and Allergan reported similar safety and efficacy for their trastuzumab biosimilar ABP980 when compared with trastuzumab in a randomized phase III study that enrolled 725 patients with HER2/neu breast cancer. Similarly, the immunogenicity of both agents was not statistically different (NCT01901146). Biocad presented a comparative pharmacokinetic study at ASCO 2014. Pharmacokinetic and safety data after a single infusion of BCD022 and trastuzumab to patients with HER2/neu (+) breast cancer were considered similar (NCT01764022) [31].

6.2 Rituximab

Rituximab (MabThera™, Rituxan™; Biogen IDEC, Cambridge, MA, USA & Genentech, South San Francisco, CA, USA; Hoffmann-La Roche, Basel, Switzerland, Canada and EU) is a genetically engineered chimeric

Table 2 Clinical trials evaluating biosimilars for a hematology/oncology indication

ClinicalTrials.gov registration number	Title	Study status	Sponsor	Start date	End of study
NCT02149524	A Study to Compare the effect of SB3 and Herceptin in Women with HER2neu Positive Breast Cancer	Active, not recruiting	Samsung Bioepis, Co., Ltd.	26 May 2014	November 2016
NCT02140736	Epoetin Alfa Biosimilar in the Management of Chemotherapy-Induced Symptomatic Anemia in Hematology and Oncology	Completed	Hospira, Inc.	September 2009	August 2011
NCT02754882	A Study Comparing SB8 and Avastin in Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer	Active	Samsung Bioepis, Co., Ltd.	June 2016	December 2018
NCT01626547	Biosimilar Retacrit (Epoetin Zeta) in the Treatment of Chemotherapy-Induced Symptomatic Anemia in Hematology and Oncology	Completed	Hospira, Inc.	December 2010	July 2013
NCT01459653	Multi-Level Evaluation of Chemotherapy-Induced Febrile Neutropenia Prophylaxis, Outcomes, and Determinants With Granulocyte-colony Stimulating Factor	Completed	Sandoz	March 2010	August 2013
NCT02158169	Biosimilar Retacrit in the Treatment of Chemotherapy-Induced Anemia in Oncology and Haematology	Completed	Hospira, Inc.	June 2012	December 2014
NCT02771795	A Long-Term Follow-up Study for Cardiac Safety in the Patients With HER2 (+) Breast Cancer Who Have Completed the SB3-G31-BC	Enrolling	Samsung Bioepis, Co., Ltd	April 2016	December 2021
NCT02768714	Trial to Compare the Efficacy and Safety of Pegfilgrastim Biosimilar in Subjects with High Risk Stage Breast Cancer Receiving Chemotherapy	Not yet recruiting	Eurofarma Laboratorios S.A.	April 2017	October 2019
NCT02069704	Bioequivalence Study Bevacizumab Biosimilar (BEVZ92) versus Bevacizumab (Avastin) in First-Line Treatment of patients with metastatic Colorectal Carcinoma	Completed	mAbxience S.A./Laboratorio Elea S.A.	October 2014	October 2015
NCT02921191	Descriptive Analysis of G-CSF Use in Patients with Breast Cancer, Lung Cancer, or Lymphoma Treated	Active, not recruiting	Biologics and Biosimilars Collective Intelligence Consortium/Amgen	January 2008	February 2017
NCT02806791	Efficacy of Biosimilar Filgrastim on the Mobilization of Hematopoietic Stem Cell CD34+ (Cluster of Differentiation 34) and on the Kinetic Engraftment	Active, Not recruiting	Azienda Ospedaliera San Giovanni Battista	May 2016	Null
NCT02454530	Use of Biosimilar Nivestim® to Prevent Chemo-Induced Neutropenia. Real Life Study	Active, Recruiting	Pfizer/Hospira Inc.	October 2014	March 2017
NCT01439191	Study of Cipterbin used Alone or with Vinorelbine in Patients with HER2neu Overexpressed Metastatic Breast Cancer	Completed	Shanghai CP Guojian Pharmaceutical Co., Ltd.	July 2005	May 2007
NCT01764022	A Safety and Efficacy Study of BCD-022 with Paclitaxel compared to Herceptin with Paclitaxel in Her-2 neu Positive Metastatic Breast Cancer Patients	Active, not recruiting	Industry	October 2012	November 2017

Table 2 continued

ClinicalTrials.gov registration number	Title	Study status	Sponsor	Start date	End of study
NCT01763645	A Safety and Efficacy Study of BCD-021 with Paclitaxel and Carboplatin Compared to Avastin with Paclitaxel and Carboplatin in Non-Small Cell Lung Cancer	Active, not recruiting	Biocad	October 2012	December 2016
NCT02787239	Clinical Study to Compare the Efficacy and Safety of Rituximab Biosimilar HLX01 and Rituximab in Combination with CHOP in Previously untreated Patients with CD20(+) DLBCL	Recruiting	Industry	October 2015	Null
NCT02031991	A Pharmacokinetic Study Comparing PF-06439535 and Bevacizumab in Healthy Male Volunteers (REFLECTIONS B739-01)	Completed	Pfizer	January 2014	August 2014
NCT01701232	Safety and Efficacy Study of BCD-020 in Therapy for Non-Hodgkin's Lymphoma	Recruiting	Biocad	September 2011	December 2016
NCT01534949	Provide Initial Evidence of Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy to Support the Pivotal CT-P10 Therapeutic Equivalence Trial	Terminated	Celltrion	February 2012	February 2013
NCT01542944	TevaGastrim for Stem Cell Mobilization	Completed	Sheba Medical Center	February 2012	April 2016
NCT01419665	GP2013 in the Treatment of Patients With Previously Treated, Advanced Follicular Lymphoma	Active, not recruiting	Sandoz/Novartis Pharmaceuticals	December 2011	March 2018
NCT02187744	A Study Of PF-05280014 Or Trastuzumab Plus Taxotere® and Carboplatin In HER2 Positive Breast Cancer In the Neoadjuvant Setting (REFLECTIONS B327-04)	Completed	Pfizer	September 2014	March 2016
NCT01121237	MONITOR-CKD5 - Multi-level Evaluation of Anaemia Treatment, Outcomes, and Determinants in Chronic Kidney Disease Stage 5	Completed	Sandoz/Hexal AG	February 2010	November 2014
NCT02522975	Biosimilar Erythropoietin in Anaemia Treatment (Correction Phase Study)	Recruiting	Shenyang Sunshine Pharmaceutical Co., LTD./Ecron Acunova GmbH	August 2015	August 2018
NCT02191150	Study of Haemodialysis Patients Switching From Aranesp to Biosimilar	Completed	Amgen	June 2014	May 2015
NCT02947438	Biosimilar Erythropoietin in Anaemia Treatment (Maintenance Phase Study)	Recruiting	Shenyang Sunshine Pharmaceutical Co., LTD./Ecron Acunova GmbH	December 2015	December 2018
NCT02341547	Effectiveness of a Biosimilar Epoetin Alfa in Stable "End Stage Renal Failure"	Not yet recruiting	Penang Hospital, Malaysia	February 2015	December 2015
NCT02708914	Study to Compare the Safety and Efficacy of UB-851 and Eprex®	Not yet recruiting	UBI Pharma Inc.	March 2016	NA
NCT01184495	Efficacy Study of Two Formulations of Erythropoietin	Completed	Hospital de Clinicas de Porto Alegre/ State Department of Health of Rio Grande do Sul/Institute of Technology Immunobiologicals Oswaldo Cruz Foundation/ BioManguinhos	April 2008	January 2009

Table 2 continued

ClinicalTrials.gov registration number	Title	Study status	Sponsor	Start date	End of study
NCT00799019	A Prospective, Immunogenicity Surveillance Registry of Erythropoiesis Stimulating Agent (ESA) With Subcutaneous Exposure in Thailand	Active, not recruiting	Chulalongkorn University/Ministry of Health, Thailand	July 2008	June 2014

NA not applicable

Table 3 Rituximab biosimilars Adapted with permission from Generics and Biosimilars Initiative (GaBI) online [33]

Company name, country	Product name	Stage of development
Amgen, USA	ABP798	Biosimilar in active development, according to Amgen's Form 10-K for 2013. One of four biosimilars for oncology indications that Amgen is developing in collaboration with Actavis [2]
Biocad, Russia	AcellBia	Non-originator biological approved in Russia in April 2014
Celltrion/Hospira, South Korea/USA	CT-P10	Phase I trial completed [6]. Phase III trials for RA and lymphoma expected to be completed in January 2017 and February 2017/March 2018, respectively. Application submitted to EMA in November 2015
Mabion, Poland	MabionCD20	Phase III trial in lymphoma expected to be completed in June 2016
Merck, USA	MK-8808	Phase I trials in RA and lymphoma completed in December and April 2014, respectively. Phase III trial started in March 2013 but halted in June 2013
Sandoz, Switzerland	GP2013	Phase I trial in Japanese NHL patients, phase I/II trial in RA and phase III trial in lymphoma expected to be completed in March 2015, November 2015, and December 2017, respectively. Application submitted to EMA in May 2016
Shanghai Henlius Biotech, China	HLX01	Phase III trial started in March 2015
Pfizer, USA	PF-05280586	Phase I/II study in RA completed, extension study and phase III study in lymphoma expected to be completed in August 2015 and November 2016, respectively
Dr Reddy's Laboratories, India	Reditux	Reditux marketed in Bolivia, Chile, India, and Peru
Samsung BioLogics, South Korea	SAIT101	Phase III trial in RA halted in 2012

EMA European Medicines Agency, *NHL* non-Hodgkin's lymphoma, *RA* rheumatoid arthritis

mouse/human monoclonal antibody with high affinity against CD20, which is a protein primarily expressed on the surface of B lymphocytes. Rituximab destroys B lymphocytes through at least four different mechanisms [32]. MabThera™/Rituxan™ had sales of US$5.6 billion in 2015. Approved indications include hematological malignancies and autoimmune disorders. The EMA Committee for Medicinal Products for Human Use (CHMP) has recommended granting marketing authorization to Celltrion's Truxima® (rituximab), a biosimilar to Roche's MabThera™. Truxima was the second biosimilar for which approval recommendation was issued by the EMA in 2016. Approval is expected in 2017. Truxima (CT-P10) also received approval from the Korea's Ministry of Food and Drug Safety (MFDS) in November of 2016. Celltrion is planning submission to the FDA early in 2017. Several other companies are rapidly developing rituximab biosimilars through the FDA and EMA pathways while others have already received approval by regulatory agencies in Russia, India, Mexico, Chile, Peru, etc. (Table 3) [33].

6.3 Bevacizumab

Bevacizumab (Avastin™, Genentech, USA) is a recombinant humanized monoclonal antibody with high affinity against vascular endothelial growth factor-A (VEGF-A). VEGF-A is an important angiogenesis promoter. Avastin™ induces regression of existing tumor vasculature and new and recurrent blood vessel formation. These angiogenesis actions result in inhibition of tumor growth and reduction of tumor size. Avastin™ received FDA approval in February 2004 and EMA approval in January 2005 [34].

Avastin™ had US$6.9 billion sales in 2015, making it one of the top biological blockbusters in medicine. Several companies are developing biosimilars to Avastin™. Of them, Amgen/Allergan developed ABP215, which completed phase III clinical evaluation in September 2015 and was accepted for review by the FDA on 15 November 2016. A randomized, double-blind study of ABP215 and Avastin™ in patients with advanced non-small cell lung cancer was completed in July 2015 (NCT01966003). The overall response rate was 39% for ABP215 ($n = 128$) and 41.7% for Avastin™ ($n = 131$). All safety and immunogenicity endpoints were similar between both agents. There were no neutralizing antibodies [35]. Samsung Bioepis (South Korea) is developing biosimilar SB8. A randomized, double-blind, three-arm, parallel-group, single-dose study comparing the pharmacokinetics, safety, tolerability, and immunogenicity of three formulations of bevacizumab (SB8, EU-sourced Avastin™, and US-sourced Avastin™) in healthy male subjects was completed in September 2015 (NCT02453672). A phase III trial evaluating the safety and efficacy of SB8 compared with bevacizumab in patients with non-squamous non-small cell lung carcinoma is ongoing and expected to complete accrual in November 2018 (NCT02754882). Pfizer is developing bevacizumab biosimilar PF-06439535 and a phase III randomized, double-blind frontline clinical trial for patients with non-small cell lung cancer comparing carboplatin/paclitaxel/bevacizumab with carboplatin/paclitaxel/PF-06439535 commenced in February 2015 and is expected to complete accrual in January 2018 (NCT02364999). At least three other companies are developing bevacizumab biosimilars and are in earlier stages of their process [36].

7 Perceptions of Biosimilars

The perception of physicians, pharmacists, payors, and patients is critical to the successful introduction of biosimilars to our daily practice. Large educational efforts by media, medical societies, the pharmaceutical industry, and patient advocacy groups have been implemented to disseminate information about the field of biosimilars and its benefits. Similarly, continuous evaluations of the impact of those educational activities are important to best understand and address lingering deficiencies in the understanding of biosimilars. One of the most commonly referenced surveys evaluating the understanding of biosimilars by healthcare providers involved 277 healthcare providers attending the 16th National Comprehensive Cancer Network annual meeting on 10–11 March 2011 [37]. It explored the familiarity of the attendees with biosimilars. Forty-seven percent of the respondents were physicians, followed by nurses (26%), and pharmacists (14%). Over one-half of the respondents (55%) were either not familiar (36%) or slightly familiar (19%) with biosimilars. However, despite their lack of familiarity with these compounds, a majority of physicians expressed either high (29%) or moderate interest (39%) in prescribing them. While this survey was applied in the early stages of developing biosimilar guidelines in the USA and knowledge regarding biosimilars and their approval pathways was not widely disseminated, subsequent opinion surveys have continued to reflect apprehension regarding prescribing biosimilars to cancer patients. During a recent biosimilars meeting, a baseline survey among 60 hematology and oncology physicians addressing familiarity revealed that 25% were still slightly familiar with biosimilars, 49% were moderately familiar, and 26% felt very familiar with the topic (personal experience). The difference in this single specialty survey likely reflects the widespread education among hematology–oncology physicians launched after the US approval of the first biosimilar for the specialty.

A recent 19-question survey was sponsored by the Biosimilar Forum[2] and conducted by an independent company (SERMO) among 1201 US physicians. The target population included physicians who prescribed biologicals from different specialties, including medical oncology, nephrology, dermatology, gastroenterology, hematology and oncology, and rheumatology. The survey took place between 20 November 2015 and 4 January 2016. When given a list of drugs, between 62.8% (medical oncologists) and 92% (dermatologists) of all surveyed were able to accurately identify biologicals. When asked how long biosimilars had been available in the US, only between 34.5% (rheumatologists) and 59% (hematology–oncology) of the respondents answered correctly. Of note, the first US biosimilar (Zarxio™; filgrastim-sndz) was approved on 6 March 2015 and was available in September 2015, two months before the survey. Furthermore, Zarxio™ has a hematology–oncology label and was not pertinent to other specialties. Approximately 75% of the surveyed physicians trust the FDA and only a minority (13%) would like to be an active part of the decision process regarding use of biosimilars in clinical practice. Approximately 80% were not aware of an association between interchangeability and autonomy for pharmacists to switch between the parental biological and its biosimilar. Between 34.5% (rheumatologists) and 57% (hematology–oncology) believe biosimilars are safe and appropriate to use in naïve and established patients. Finally, when asked if biosimilars will be less safe than the reference products due to the

[2] The biosimilar forum is a network of pharmaceutical companies including Allergan, Amgen, Boehringer-Ingelheim, Coherus, EMD-Serono, Merck, Pfizer, Samsung Bioepis, Sandoz, and Teva.

Table 4 Potential challenges for full acceptance of biosimilars in cancer medicine

Approving regulatory agency (EMA, FDA, etc.)
Sponsor disclosure of data leading to biosimilar approval
Sponsor's track record in drug development
Safety and efficacy data for specific biosimilar application/label
Physician education
Physician's experience with the approved product
Pharmacovigilance programs and post-marketing safety
Endorsement/adoption by national health services, payors, health systems
Commercial cost compared with originator product

EMA European Medicines Agency, *FDA* US Food and Drug Administration

abbreviated approval pathway, a minority of physicians (28.5% [hematology–oncology] to 48% [rheumatologists] [average 35.9%]) believed they were less safe. The responses in this survey also established that the most common areas of interest were "safety, efficacy, and potency of biosimilars", "interchangeability/substitutability", and "cost of biosimilars" [38]. While Cohen et al. [38], for the Biosimilars Forum, reported substantial improvement in the perception of biosimilars in medicine, ongoing education is still critical to overcome other potential existing challenges to reaching complete acceptance of biosimilars in cancer medicine (Table 4).

8 Conclusions

Following the European experience developing and implementing regulatory pathways for the approval of biosimilars, the FDA rapidly advanced its guidelines in the US, leading to the approval of the first four biosimilars by November 2016. While the field of biosimilars in cancer medicine is young, large educational efforts have gradually but substantially overcome early apprehension expressed by physicians' surveys regarding the safety and efficacy of incorporating biosimilars into cancer care. Beyond healthcare educational programs, I believe that building trust for biosimilars among physicians and patients is critical for the successful adoption of these new biologicals in cancer care.

Cost savings are a major incentive for the adoption of biosimilars. The European experience predicts approximately 30–45% cost cuts for biologicals by adopting biosimilars. However, standardization in the naming and approval processes worldwide are a major need in this field. Clinical trial designs, number of patients enrolled in those studies, medical conditions studied, and the rigor of the results analysis by regulatory agencies will also be critical aspects to satisfy an expectant audience looking for reassurance regarding the similarity of patient clinical outcomes. Additionally, policies educating and encouraging healthcare providers and patients to report post-marketing adverse events will further improve the safety monitoring of biosimilars by sponsors and governmental agencies and increase the trust among patients and providers. Importantly, novel and improved biosimilar pharmacovigilance strategies represent a great opportunity to improve the current guidelines in place for their originator counterparts. Strong pharmacovigilance programs will determine successful monitoring measures and describe early signals of safety concern. The development and improvement of those programs remain challenging.

Compliance with Ethical Standards

Funding Dr. Camacho receives research funds from Macrogenics, Inc.

Conflicts of Interest Dr. Camacho is a member of the bureau of speakers of Amgen, Merck, and Lexicon.

References

1. Camacho LH, Frost CP, Abella E, Morrow PK, Whittaker S. Biosimilars 101: considerations for U.S. oncologists in clinical practice. Cancer Med. 2014;3(4):889–99. doi:10.1002/cam4.258.
2. FDA. FDA 101: regulating biological products. 25 July 2008. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048341.htm. Accessed 15 Sept 2016.
3. Schneider CK. Biosimilars in rheumatology: the wind of change. Ann Rheum Dis. 2013;72(3):315–8. doi:10.1136/annrheumdis-2012-202941.
4. FDA. Frequently asked questions on patents and exclusivity. What is the difference between patents and exclusivity? 2014. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm. Accessed 15 Sept 2016.
5. Generic Pharmaceutical Association. Generic drug savings in the U.S. Seventh annual edition: 2015. http://www.gphaonline.org/media/wysiwyg/PDF/GPhA_Savings_Report_2015.pdf. Accessed 16 Dec 2016.
6. Camacho LH, Pai N. Pharmacovigilance of oncology biosimilars. J Pharmacovigil. 2015;S3(001):1–6. doi:10.4172/2329-6887.S3-001.
7. GaBi. WHO definitions of biosimilars. In: Generics and Biosimilars Initiative Journal (GaBI Journal). gabionline.net. 2012. http://gabionline.net/Biosimilars/General/WHO-definitions-of-biosimilars. Accessed 21 Sept 2016.
8. FDA. Nonproprietary naming of biological products - guidance for industry. 2015. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf. Accessed 13 Oct 2016.
9. FDA. Guidance for industry - reference product exclusivity for biological products filed under Section 351(a) of the PHS Act. 2014. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm407844.pdf. Accessed 30 Sept 2016.
10. FDA. Scientific considerations in demonstrating biosimilarity to a reference product. FDA, 2015. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed 26 Oct 2016.

11. FDA. Guidance for industry - clinical pharmacology data to support a demonstration of biosimilarity to a reference product. 2014. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf. Accessed 1 March 2017.
12. WHO. Essential medicines and health products - pharmacovigilance. 2016. http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/. Accessed 4 Oct 2016.
13. Chabner BA, Longo DL. Cancer chemotherapy and biotherapy—principles and practice. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.
14. Niederwieser D, Schmitz S. Biosimilar agents in oncology/haematology: from approval to practice. Eur J Haematol. 2011;86(4):277–88. doi:10.1111/j.1600-0609.2010.01566.x.
15. FDA. Interferon alfa-2b package insert. In: FDA approved drug products. 1986. https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory-labelinfo. Accessed 16 Sept 2016.
16. FDA. Filgrastim package insert. 2014. https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory-labelinfo. Accessed 26 Sept 2016.
17. EMA. European Medicines Agency biosimilar approvals guidelines. 2005. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Accessed 12 Dec 2016.
18. Biosimilar N. 10 years of biosimilar medicines in Europe: transforming healthcare. 2016. http://www.biosimilarnews.com/10-years-of-biosimilar-medicines-in-europe-transforming-healthcare. Accessed 28 Nov 2016.
19. Troy DE. Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) testimony before the Senate Committee on the Judiciary. 1 Aug 2003. Updated 24 Jul 2009. https://www.fda.gov/newsevents/testimony/ucm115033.htm. Accessed 12 April 2017.
20. FDA. Biosimilars implementation. In: Committee on Energy and Commerce-Subcommittee on Health-United States House of Representatives. FDA, 2016. http://www.fda.gov/newsevents/testimony/ucm485042.htm. Accessed 12 Sept 2016.
21. WHO. Guidelines on the use of International Nonproprietary Names (INNs) for pharmaceutical substances. Geneva: Programme on International Nonproprietary Names (INN); 1997. http://apps.who.int/medicinedocs/pdf/h1806e/h1806e.pdf. Accessed 21 Nov 2016.
22. WHO. Guidance on INN. WHO, 2015. http://www.who.int/medicines/services/inn/innguidance/en/. Accessed 11 Oct 2016.
23. Murphy B. Debate over naming of biosimilars intensifies ahead of WHO meeting. Pharm J. 2015;294(7866). doi:10.1211/PJ.2015.20068663.
24. Brennan Z. FDA calls on companies to select 10 suffixes for biosimilar, biologic names. Rockville: Regulatory Affairs Professionals Society (RAPS); 2016.
25. Siegel JF, Fischer A. Ten years of biosimilars in Europe. Biologics Blog. 2015 Dec 8. http://www.biologicsblog.com/ten-years-of-biosimilars-in-europe/. Accessed 12 April 2017.
26. EMA. Guideline on similar biological medicinal products. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf. Accessed 16 Nov 2016.
27. Genentech. Trastuzumab: package insert and prescribing information. 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103792s5327lbl.pdf. Accessed 6 Nov 2016.
28. GaBI. Celltrion submits trastuzumab biosimilar application to EMA. Generics and Biosimilars Initiative. 2016. http://www.gabionline.net/Biosimilars/News/Celltrion-submits-trastuzumab-biosimilar-application-to-EMA. Accessed 21 Nov 2016.
29. Rugo HS, Barve A, Waller CF, Hernandez-Bronchud M, Herson J, Yuan J, et al. Heritage: a phase III safety and efficacy trial of the proposed trastuzumab biosimilar Myl-1401O versus Herceptin [abstract no. LBA503]. J Clin Oncol. 2016;34 suppl.
30. Yin D, Barker KB, Li R, Meng X, Reich SD, Ricart AD, et al. A phase I pharmacokinetics trial comparing PF-05280014 (a potential biosimilar) and trastuzumab in healthy volunteers (REFLECTIONS B327-01) [abstract no. 612]. J Clin Oncol. 2013;31 suppl.
31. Stenina MB, Ignatova E, Frolova MA, Burdaeva ON, Nechaeva MP, Kopp MV, et al. Pharmacokinetics and safety of BCD-022, trastuzumab biosimilar candidate, compared to Herceptin in patients [abstract no. e11576]. J Clin Oncol. 2014;32 suppl.
32. Genentech. Rituximab: package insert-prescribing information. 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103705s5432lbl.pdf. Accessed 16 Nov 2016.
33. GaBI. Biosimilars of rituximab. In: Generics and Biosimilars Initiative Journal (GaBI Journal). 2015. http://gabionline.net/Biosimilars/General/Biosimilars-of-rituximab. Accessed 21 Nov 2016.
34. Genentech. Bevacizumab: package insert-prescribing information. 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125085s305lbl.pdf. Accessed 16 Nov 2016.
35. Thatcher N, Thomas M, Paz-Ares L, Ostoros G, Pan Z, Goldschmidt JH, et al. Randomized, double-blind, phase 3 study evaluating efficacy and safety of ABP 215 compared with bevacizumab in patients with non-squamous NSCLC [abstract no. 9095]. J Clin Oncol. 2016;34 suppl.
36. GaBI. Biosimilars of Bevacizumab. In: Generics and Biosimilars Initiative Journal (GaBI Journal). 2016. http://www.gabionline.net/Biosimilars/General/Biosimilars-of-bevacizumab. Accessed 25 Nov 2016.
37. Zelenetz AD, Ahmed I, Braud EL, Cross JD, Davenport-Ennis N, Dickinson BD, et al. NCCN Biosimilars White Paper: regulatory, scientific, and patient safety perspectives. J Natl Compr Cancer Netw. 2011;9(Suppl 4):S1–22.
38. Cohen H, Beydoun D, Chien D, Lessor T, McCabe D, Muenzberg M, et al. Awareness, knowledge, and perceptions of biosimilars among specialty physicians. Adv Ther. 2017;33(12):2160–72. doi:10.1007/s12325-016-0431-5.
39. GaBI. Biosimilars approved in Europe. GaBI; 2016. http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe. Accessed 28 Nov 2016.