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New Drugs

A clinician's guide to biosimilars in oncology

Hope S. Rugo [a,*], Kim M. Linton [b], Paul Cervi [c], Julie A. Rosenberg [d], Ira Jacobs [e]

[a] University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, USA
[b] The University of Manchester, Centre for Haematological Oncology, Manchester, UK
[c] Southend University Hospital NHS FT, Southend, UK
[d] Pfizer Inc, Groton, CT, USA
[e] Pfizer Inc, New York, NY, USA

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ABSTRACT

Biological agents or "biologics" are widely used in oncology practice for cancer treatment and for the supportive management of treatment-related side effects. Unlike small-molecule generic drugs, exact copies of biologics are impossible to produce because these are large and highly complex molecules produced in living cells. The term "biosimilar" refers to a biological product that is highly similar to a licensed biological product (reference or originator product) with no clinically meaningful differences in terms of safety, purity, or potency. Biosimilars have the potential to provide savings to healthcare systems and to make important biological therapies widely accessible to a global population. As biosimilars for rituximab, trastuzumab, and bevacizumab are expected to reach the market in the near future, clinicians will soon be faced with decisions to consider biosimilars as alternatives to existing reference products. The aim of this article is to inform oncology practitioners about the biosimilar development and evaluation process, and to offer guidance on how to evaluate biosimilar data in order to make informed decisions when integrating these drugs into oncology practice. We will also review several biosimilars that are currently in development for cancer treatment.

Introduction

New agents for the treatment and supportive care of cancer have markedly improved therapeutic options and outcome for many malignancies. Biologics include monoclonal antibodies (mAbs) targeted to critical pathways involved in cancer pathogenesis and growth factors to reduce or ameliorate treatment-related hematological toxicity. Unfortunately, access to potentially life-saving biologics is limited in many areas of the world [1–3]. As the patent expiry of several drugs approaches, there has been intense interest in developing biosimilar agents to introduce cost savings for healthcare systems and to widen global access to key biological therapies [1,2,4].

A biosimilar drug is a biological product that is highly similar, but not identical, to a licensed biological product (the reference or originator product) [5–7]. Unlike small-molecule generic drugs that are typically chemically synthesized and easy to replicate, it is impossible to make exact copies of reference products because biosimilars (as biologics) are large and highly complex molecules produced in living cells. Structural differences to the reference product may arise due to variations in post-translational modification (such as glycosylation patterns), which could have impact upon drug efficacy or safety [5–7]. The development of biosimilars therefore involves extensive evaluation and a detailed, comprehensive manufacturing process to ensure that there are no clinically meaningful differences in purity, safety, or potency [5–7]. As is the case for any new therapeutic agent, the evaluation process and approval requirements for a proposed biosimilar may differ between regulatory agencies, leading to differential access based on geographic location.

Drugs for supportive care were the first biosimilars to gain approval for use, with the European Union (EU) approval in 2007 of epoetin alfa and filgrastim [8]. The first biosimilar approved in the United States (US) was filgrastim in 2015 [9]. Patents for several biologic mAbs for cancer treatment have recently expired in the EU and will soon expire in the US (see Table 1 for products and patent expiration dates). This has instigated multiple biosimilar development programs and regulatory approval requests for newly developed biosimilar agents. Biosimilars for rituximab,

* Corresponding author at: University of California San Francisco Comprehensive Cancer Center, 1600 Divisadero St, San Francisco, CA 94115, USA. Tel.: +1 415 353 7618; fax: +1 415 353 9571.
E-mail addresses: Hope.Rugo@ucsf.edu (H.S. Rugo), Kim.M.Linton@manchester.ac.uk (K.M. Linton), Paul.Cervi@southend.nhs.uk (P. Cervi), JulieAnn.Rosenberg@pfizer.com (J.A. Rosenberg), Ira.Jacobs@pfizer.com (I. Jacobs).

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Table 1
Biosimilar mAbs with registered phase III clinical trials for oncology.[a]

Reference product	Patent expiration in EU/US	Biosimilar	Manufacturer	Primary endpoint	Condition	Published data[b]
Trastuzumab (Herceptin®, Genentech)	2014/2019	BCD-022	Biocad	ORR	HER2+ MBC	*Phase I:* BCD-022 showed similar PK and safety to trastuzumab in patients with HER2+ MBC [33]
		PF-05280014	Pfizer	PK, pCR (2nd) ORR	HER2+ EBC HER2+ MBC	*Preclinical:* PF-05280014 showed similar structural and functional properties, PK and immunogenicity profiles to trastuzumab [34] *Phase I:* PF-05280014 showed similar PK, safety and immunogenicity to trastuzumab in healthy volunteers [35]
		ABP 980	Amgen	ORR	HER2+ EBC	*Phase I:* ABP 980 showed comparable PK, PD, safety, tolerability and immunogenicity to trastuzumab in healthy volunteers [36]
		CT-P6	Celltrion	pCR pCR	HER2+ EBC HER2+ MBC	*Phase I/IIB:* CT-P6 showed equivalent PK and similar safety to trastuzumab in patients with HER2+ MBC [37] *Phase III:* CT-P6 showed similar efficacy (ORR) and safety to trastuzumab in combination with paclitaxel [38]
		SB3-G31-BC	Samsung Bioepis	pCR	HER2+ BC	No published data
		Hercules/ Myl1401O	Mylan GmbH	ORR	HER2+ MBC	No published data
Rituximab (Rituxan®, Genentech/Biogen Idec; MabThera®, Roche)	2013/2016	GP2013	Sandoz	ORR	FL	*Preclinical:* GP2013 showed physicochemical and functional characteristics comparable to rituximab [39] *Preclinical:* GP2013 showed similar in vitro potency and similar PK, PD, and efficacy to rituximab [40]
		BCD-020	Biocad	CD20+ count ORR	Indolent NHL	*Phase III:* BCD-020 showed equivalent PK and similar PD and safety to rituximab in patients with indolent NHL [41] *Phase III:* BCD-020 showed similar efficacy (ORR) and safety to rituximab in patients with indolent B-cell non-Hodgkin's lymphoma [42]
		PF-05280586	Pfizer	ORR	LTBFL	*Preclinical:* PF-05280586 showed similar structural and in vitro functional characteristics and similar in vivo PK and immunogenicity profiles to rituximab [43] *Phase I:* PF-05280586 showed similar PK, effectiveness, and safety to rituximab in subjects with active rheumatoid arthritis [44]
		CT-P10	Celtrion	ORR	FL	*Phase III:* CT-P10 showed equivalent PK and similar efficacy (ACR20/50/70), PD, safety [45], and immunogenicity [46] to rituximab in subjects with rheumatoid arthritis
		RTXM83	mAbxience	ORR	DLBCL	*Preclinical:* RTXM83 showed similar structural and in vitro functional characteristics and similar in vivo PK/PD profiles to rituximab [47] *Phase III:* RTXM83 showed comparable PK and safety profile (immunogenicity) to rituximab when combined with CHOP for first-line treatment of DLBCL [48]
		ABP 798	Amgen	RD, ORR	NHL	No published data
Bevacizumab (Avastin®, Genentech)	2022/2019	BCD-021	Biocad	ORR	NSCLC	*Phase I:* BCD-021 showed similar PK and safety to bevacizumab in patients with NSCLC [49] *Phase III:* BCD-021 showed similar efficacy (ORR), safety and immunogenicity to bevacizumab in patients with advanced non-squamous NSCLC [50]
		PF-06439535	Pfizer	ORR	NSCLC	*Preclinical:* PF-06439535 showed similar structure and in vitro biological activity [51] and similar in vivo toxicologic and toxicokinetic to bevacizumab [52–54] *Phase I:* PF-06439535 demonstrated PK similarity and comparable safety profiles to bevacizumab [53]
		ABP 215	Amgen	ORR	NSCLC	*Preclinical and Phase I:* ABP 215 showed similar in vitro functional characteristics and equivalent human PK to bevacizumab

DLBCL, diffuse large B-cell lymphoma; EBC, early breast cancer; FL, follicular lymphoma; HER2+, human epidermal growth factor receptor 2–positive; LTBFL, low tumor burden follicular lymphoma; MBC, metastatic breast cancer; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; ORR, overall response rate; pCR, pathological complete response; PD, pharmacodynamics; PK, pharmacokinetics; RD, risk difference.

[a] Registered on ClinicalsTrials.gov, the International Clinical Trials Registry Platform, or the European Union Clinical Trials Register.

[b] Published on PubMed, Web of Science, or congress websites.

trastuzumab, and bevacizumab are expected to reach the market in the near future, and clinicians will soon be faced with decisions to utilize biosimilars as alternatives to existing reference products. The aim of this article is to inform oncology practitioners about the biosimilar development and evaluation process, including relevant clinical trial design issues, and to enable critical appraisal of data to allow for best informed decision making when integrating biosimilars into practice.

Regulatory requirements for approval of biosimilars in oncology

Biosimilarity is confirmed when "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and 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" [6]. The regulatory requirements for establishing biosimilarity are science-based and generally similar for the European Medicines Agency (EMA), US Food and Drug Administration (FDA), and World Health Organization (WHO) [5–7]. The approval process for biosimilars includes extensive comparisons between the proposed biosimilar and the reference biological agent to assess overall similarity (Fig. 1). A stepwise process starts with an analytical and nonclinical comparison of structural and in vitro functional characteristics and in vivo animal studies, including assessments of toxicity. The extent and nature of data required at each step depends on the level of evidence obtained in the preceding steps. The type and amount of data considered to be sufficient to demonstrate biosimilarity is also determined on a product-specific basis. Final approval is dependent on one or more comparative clinical studies in an appropriate clinical setting, with at least one study including an assessment of immunogenicity and pharmacokinetics [PK] or pharmacodynamics [PD] demonstrating safety, purity, and clinical efficacy of the biosimilar.

Data required to demonstrate biosimilarity

The goal of the biosimilar development program is to demonstrate high similarity to the reference product. Due to the complexity of biologics and the lack of access to proprietary manufacturing data, developers reverse engineer the reference product to create a biological product (biosimilar) that is highly similar to it.

Table 2
Studies to demonstrate structural and functional similarity between a proposed biosimilar and trastuzumab.

Study	Purpose
In vitro studies to demonstrate physicochemical similarity	
Liquid chromatography/mass spectrometry for peptide mapping	To compare the sequence of amino acids that constitutes the primary structure
N-linked oligosaccharide profiling/glycan patterns	To compare glycosylation patterns resulting from post-translational modifications
Imaged capillary isoelectric focusing	To detect charged isoforms heterogeneity
Size exclusion HPLC	To compare the degree of purity in terms of the levels of monomer and high molecular mass species
In vitro studies to demonstrate functional similarity	
Inhibition of tumor cell growth	To demonstrate similar inhibition of HER2-expressing cell growth
Antibody-dependent cell-mediated cytotoxicity	To demonstrate similar ability to induce cell death by binding to natural killer cells
HER2 binding assay	To demonstrate that the biosimilar exert
Fcγ RIIIa binding assay	its clinical activity through the same mechanism of action as trastuzumab

FcγRIIIa, cell surface receptor for immunoglobulin G Fc; HER2+, human epidermal growth factor receptor 2–positive; HPLC, high-performance liquid chromatography.

Nonclinical in vitro studies

The basis for establishing biosimilarity involves an extensive physicochemical and biological characterization. Hence, the nonclinical in vitro program has to include robust analytical techniques along with sensitive biochemical and functional assays to detect any potential variability between the reference product and the biosimilar. Table 2 shows examples of studies conducted to demonstrate structural and in vitro functional similarity of proposed biosimilars to trastuzumab (Herceptin®, Genentech Inc, South San Francisco, CA), a humanized recombinant mAb targeting

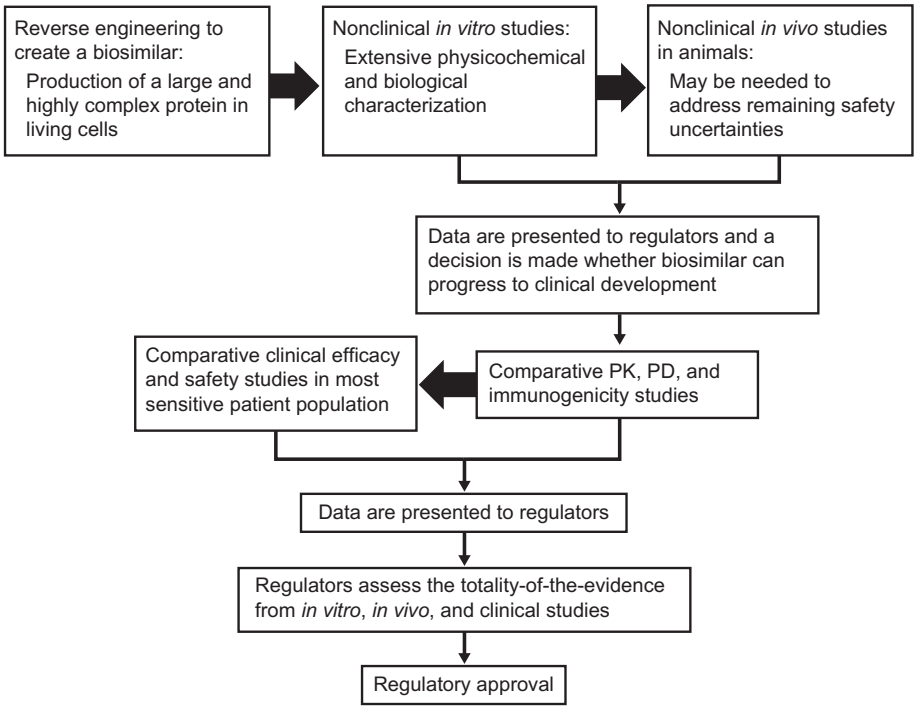

Fig. 1. The biosimilar development process.

cancer cells overexpressing the human epidermal growth factor receptor 2 (HER2), and approved in the US and the EU for treatment of HER2+ breast and gastric cancers. Differences between a proposed biosimilar and trastuzumab detected by any of these analyses may affect the binding, biological activity, immunogenicity or patient safety.

Nonclinical in vivo studies

The nonclinical in vivo program follows a stepwise approach recommended by the EMA, FDA, and WHO [6,7,10]. According to EMA guidelines, based on the outcome of the extensive structural and functional comparisons, a decision will be made to determine the need for in vivo studies in animals and, if so, the extent and focus of these studies [5]. Animal studies may be needed to address remaining uncertainties about safety and to provide additional evidence before advancing to clinical studies in humans. It should be noted that different strategies may be applied to the nonclinical development of different biosimilars, depending on what is known about the development program of the reference product. Based on the totality of evidence (i.e. consideration of the quantity and quality of the evidence to support biosimilarity) from the nonclinical program, a decision is then made about whether to continue with the development of the biosimilar and to proceed to clinical studies.

Clinical studies

The goal of the clinical program is not to demonstrate clinical efficacy per se, as this was established for the reference product, but to address any residual uncertainty about biosimilarity after conducting physicochemical and biological characterization and, where appropriate, animal studies [5,6]. Comparative clinical studies are conducted to demonstrate similarity between the biosimilar and the reference product in a stepwise manner beginning with PK, PD (if relevant markers exist), and immunogenicity studies followed by comparative clinical efficacy and safety (including immunogenicity) study/studies. The extent of clinical evaluations may depend on the degree of biosimilarity shown in the nonclinical phase [5,6].

Biosimilar mAbs in development for cancer treatment

Many biosimilar mAbs are currently in development for the treatment of cancer (Table 1). Specific requirements for the clinical development of biosimilars in oncology are based on the approval process of the reference product and are developed with regulatory input. The EMA guidelines for biosimilar mAbs licensed for oncology indications stipulate that the most sensitive patient population and clinical endpoints should be used to detect differences in efficacy and safety between a biosimilar and a reference product [11]. The guidelines further recommend using a homogeneous patient population and an endpoint that measures activity, such as overall response rate (ORR), ORR at a certain time point, or pathological complete response (pCR) [11]. The biosimilars shown in Table 1 have completed their preclinical assessments and, based on the totality of evidence, progressed to clinical testing. However, oncologists should be aware that in some countries several non-comparable copies of biological products (sometimes called 'intended copies') have been introduced without the proper demonstration of biosimilarity to a licensed reference product and without approval via a regulatory pathway aligned with EMA, FDA, or WHO guidelines [12–14]. Biologics with unknown quality and clinical profile may pose an increased risk to patient safety and may not demonstrate clinical efficacy [14].

Factors that may influence the integration of biosimilars into oncology practice

Patient population for efficacy evaluation

Regulatory guidelines recommend using the most sensitive patient population in clinical biosimilar trials so that potential differences in efficacy, safety, and/or immunogenicity could be attributed to the drug itself and not the patient population [11]. In the case of trastuzumab, clinical studies to demonstrate biosimilarity are being conducted in settings in which trastuzumab has demonstrated efficacy: in early breast cancer (EBC) as neoadjuvant therapy, and as first-line treatment for metastatic breast cancer (MBC) [15–24]. Both settings have advantages and disadvantages, with longer treatment required in the metastatic setting, but less data on long-term efficacy and safety in the neoadjuvant setting. In the case of rituximab, clinical studies to demonstrate biosimilarity are underway in the appropriate histologic subtypes of non-Hodgkin's lymphoma, including both low grade and high grade disease. Most clinical studies designed to demonstrate biosimilarity to bevacizumab are being conducted in patients with previously untreated advanced non-small-cell lung cancer, a population with a well categorized safety and efficacy profile for treatment with bevacizumab in combination with paclitaxel and carboplatin.

Efficacy endpoints

The primary endpoints of a biosimilar clinical trial will usually be chosen to detect clinically relevant differences between the proposed biosimilar and the reference product, and it is important to note that the endpoints may be different to those used for the approval of the reference product. Recognizing that the preferred endpoint to prove efficacy in cancer, e.g. progression-free survival (PFS) or overall survival, may not be feasible or sensitive enough to demonstrate biosimilarity between a proposed biosimilar and the reference product, the EMA recommends using a clinical endpoint that measures activity as primary endpoint, such as ORR or pCR [11]. Meta-analyses of trastuzumab clinical trials data suggested that pCR in the neoadjuvant HER2+ setting is a sensitive efficacy endpoint to establish initial similarity, as is ORR in the first-line metastatic setting [25]. Accordingly, for trastuzumab biosimilars, both pCR and ORR may be used as primary endpoints in clinical comparative studies. For rituximab biosimilars, all ongoing clinical comparative studies use ORR as a primary endpoint; however, this is a primary endpoint that was not used in clinical trials for the reference product rituximab. ORR is also the primary endpoint in clinical studies designed to demonstrate biosimilarity to bevacizumab.

Extrapolation of indication

Because the clinical portion of the comparability exercise between a biosimilar and its reference product is typically limited to one or two phase III comparative clinical trials, some physicians may be concerned about using the biosimilar for indications in which it has not been studied but for which the reference product is approved. This is referred to as extrapolating data from clinical studies in one medical condition to support another medical condition. EMA, FDA, and WHO regulatory guidelines allow extrapolation of indications when there is sufficient scientific justification and the totality of evidence demonstrates biosimilarity and known mechanism of action [6,7,10]. Nonetheless, there are ongoing discussions regarding the best setting to demonstrate biosimilarity of efficacy and safety that will allow indication extrapolation.

The first biosimilar mAb (marketed as Remsima® and Inflectra®) approved by EMA was granted approval for all indications of the

reference product, infliximab (Remicade®). Because infliximab is indicated for a variety of medical conditions (Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis), there was a debate about the data required to allow indication extrapolation. However, the EMA granted approval to all indications not only based on the two comparative clinical studies conducted in patients with ankylosing spondylitis and rheumatoid arthritis, but also on the similarity demonstrated in the preclinical program (analytical and functional in vitro studies), nonclinical in vivo and clinical phase I studies, and on the known main mechanism of action [26,27].

Rituximab has the largest market of any monoclonal antibody agent, and clinicians have raised similar concerns about extrapolating data from clinical studies of rituximab biosimilars in rheumatoid arthritis to non-Hodgkin lymphoma (NHL), and from one NHL clinical setting to another, including different histological subtypes, palliative versus curative strategies, and monotherapy versus combination (with chemotherapy) regimens. For example, clinical studies to demonstrate biosimilarity are underway in appropriate histological subtypes of NHL for which rituximab is approved [25], but are investigating these agents in first-line treatment of indolent NHL even though rituximab monotherapy is not approved in the EU or the US for the first-line treatment of follicular lymphoma [26]. While the monotherapy design was deliberately chosen to allow assessment of biosimilarity without the potentially confounding issue of combining rituximab with chemotherapy, extrapolation of indication will only be acceptable with appropriate scientific justification and if the clinically relevant mechanism of action is proved to be the same.

Trastuzumab is the standard of care for patients with HER2-positive breast cancer and clinical benefit including improved survival has been demonstrated with the addition of trastuzumab to chemotherapy in several clinical studies [8,23,28], and in both early and late stage disease. Clinical studies to demonstrate biosimilarity in the metastatic setting have used an approach in which the biosimilar is continued as a single agent after initial treatment including chemotherapy. Extrapolation to other combinations and indications can be justified if biosimilarity is established based on the totality of the evidence and the mechanism of action is shown to be the same in the different indications. Similarly, for bevacizumab, most comparative clinical studies are conducted in the fist-line setting in advanced NSCLC, a population that is well characterized and considered to be sensitive enough to detect potential differences between a proposed biosimilar and bevacizumab. Once biosimilarity is established based on the preclinical and clinical data and the mechanism of action is proved to be the same, extrapolation to other indications for bevacizumab (i.e. metastatic colorectal cancer, metastatic renal cell cancer and certain gynaecologic cancers) may be justified.

Post-approval safety monitoring

Immunogenicity is a key element in establishing biosimilarity between the proposed biosimilar and the reference product and is assessed in both nonclinical and clinical studies. However, clinically meaningful immune responses to a biological agent may develop after long-term use, with the potential to affect both the safety and efficacy of the agent. For example, a change in the manufacturing process of the originator epoetin (Eprex®, Janssen) led to increased rates of antibody-mediated pure red cell aplasia in the EU between 1998 and 2004 [29]; this further emphasizes the importance of post-approval monitoring for immunogenicity. Accordingly, the clinical safety of all biological products, including biosimilars, must be monitored on an ongoing basis during the post-approval period of use. This will enable the identification of rare but potentially serious safety risks (e.g. immunogenicity) not detected during the shorter follow-up of clinical studies [6,7,10]. Manufacturers are responsible for setting up effective post-marketing safety monitoring systems for biosimilar agents and must report adverse reactions associated with the reference product and its drug class [6,7,30]. Practicing physicians also have a central role in ensuring patient safety in this setting and are required to report any suspected adverse drug reaction and to identify the associated causative drug, be it the biosimilar or the reference product [31].

Interchangeability and automatic substitution

Interchangeability refers to the medical practice of switching from one biological agent (the reference product) to another (the biosimilar) with the expectation of producing the same clinical outcome as the reference product in any patient treated in a given clinical setting. Automatic substitution occurs when an interchangeable biological product (e.g. biosimilar) is substituted for the reference product by a pharmacist without the intervention or knowledge of the healthcare provider who prescribed the reference product. It is important to note that biosimilarity does not guarantee interchangeability. A recent recommendation from the FDA states that in order to meet the standards for interchangeability, "an applicant must provide sufficient information to demonstrate biosimilarity, and also demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch" [32]. As such, the FDA may approve interchangeability, but each state can decide whether to allow automatic substitution [32]. The EMA does not provide guidance regarding interchangeability; it is within the authority of member countries [5].

Summary and conclusions

As biosimilar mAbs begin to enter the landscape of cancer treatment, it is increasingly necessary for cancer specialists to understand the issues involved in biosimilar development to enable them to make informed decisions when integrating these drugs into their clinical practice. The goal of the biosimilar development program is to demonstrate biosimilarity to the reference product in nonclinical in vitro, nonclinical in vivo, and limited comparative clinical trials rather than to prove clinical equivalence of long-term efficacy, safety, and immunogenicity for all the approved indications of the reference product. The regulatory framework for the development of biosimilars is evolving on a global scale and robust efforts are being made to manufacture high-quality, safe, and effective biosimilar agents.

In general, oncologists will rely on the EMA/FDA review and approvals to verify that a biosimilar is highly similar to the reference product with no clinically significant differences. However, an understanding of key issues will help when integrating biosimilars into clinical practice (Table 3), albeit that in some regions, the health commissioners rather than clinicians will determine the timing of the switch to a biosimilar and the indications for use. There may be subtle differences in the chemical structure and immunogenicity compared with the reference product, which may alter the clinical response, long-term outcome or toxicity over time. Therefore, a post-marketing safety monitoring system is put

Table 3
Key issues oncologists should consider when prescribing biosimilars.

- Regulatory approval information
- Interchangeability status for FDA-approved biosimilars
- Substitution practice within their country/state
- Approved indications (including via extrapolation)
- Available safety data (including immunogenicity) – physicians play a key role in documenting any adverse drug reaction post approval.

FDA, US Food and drug administration.

in place for biologics (including biosimilars), and oncologists play a key role in documenting any adverse drug reactions.

Author contribution

All authors prepared the article and approved the final draft for submission.

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Conflicts of interest

Julie A. Rosenberg and Ira Jacobs are employees of and hold stock and stock options in Pfizer Inc. Paul Cervi received consultancy fees from Pfizer Inc, Groton, CT USA. Hope S. Rugo receives research support to UCSF for clinical trials sponsored by Pfizer (not involving biosimilars). She is the principal investigator for a biosimilar trial sponsored by Mylan but receives no compensation for this work, and receives research support through UCSF for clinical trials sponsored by Roche/Genentech. Kim M. Linton declares no competing interests.

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