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The evolution of biosimilars in oncology, with a focus on trastuzumab

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ABSTRACT

Cancer therapy has evolved significantly with increased adoption of biologic agents ("biologics"). That evolution is especially true for HER2 (human epidermal growth factor receptor-2)–positive breast cancer with the introduction of trastuzumab, a monoclonal antibody against the HER2 receptor, which, in combination with chemotherapy, significantly improves survival in both metastatic and early disease.

Although the efficacy of biologics is undeniable, their expense is a significant contributor to the increasing cost of cancer care. Across disease sites and indications, biosimilar agents are rapidly being developed with the goal of offering cost-effective alternatives to biologics. Biosimilars are pharmaceuticals whose molecular shape, efficacy, and safety are similar, but not identical, to those of the original product. Although these agents hold the potential to improve patient access, complexities in their production, evaluation, cost, and clinical application have raised questions among experts. Here, we review the landscape of biosimilar agents in oncology, with a focus on trastuzumab biosimilars. We discuss important considerations that must be made as these agents are introduced into routine cancer care.

Key Words Biosimilars, trastuzumab, Herceptin, value

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INTRODUCTION

In recent years, cancer treatment has been revolutionized by the introduction of biologic agents ("biologics"). That revolution is especially evident for HER2 (human epidermal growth factor receptor 2)–positive breast cancer with the introduction of trastuzumab, a monoclonal antibody against HER2 that significantly improves survival in both metastatic and early disease.

Although their efficacy is undeniable, expensive biologics, including trastuzumab, are a significant contributor to the increasing cost of cancer care. In developing countries, fewer than 10% of patients have access to HER2-targeted therapies, largely because of the cost[1]. In 2012, the World Health Organization released a proposal for the inclusion of trastuzumab in its list of essential medicines. Trastuzumab was subsequently added to the list in 2015, with the caveat that the petition for inclusion was based on the possibility of obtaining a lower-cost biosimilar product.

Biosimilars are pharmaceuticals whose molecular shape, efficacy, and safety are similar, but not identical, to the original product. Across disease sites and indications, biosimilar agents are rapidly being developed with the goal to create price competition and to provide cost-effective alternatives to biologics. Although these agents have the potential to improve patient access, complexities in their production, evaluation, and clinical application have raised questions among experts.

HISTORY OF BIOSIMILAR AGENTS

Compared with small-molecule drugs, biologics are larger and more complex—and therefore more susceptible to production differences. Unlike traditional small-molecule drugs for which generic versions can be produced, biologics cannot be identically copied. Biologic agents are manufactured using cell lines and processes exclusive to the manufacturer. They require multiple steps for cloning, selecting, and expanding the cell line, and then isolating and purifying the product[2]. At multiple points during that process, clinically significant alterations can potentially occur. A different cell line, for example, might result in a difference in post-translational protein modification that can affect immunogenicity and alter a drug's pharmacokinetics and dynamics.

The European Medicines Agency (EMA) was the first regulatory body to develop, in 2003, guidelines for biosimilars. In 2010, Canada adopted the guidance document

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Information and Submission Requirements for Biosimilar Biologic Drugs[3], which was updated in 2016. Also in 2010, then U.S. president Barack Obama signed into law the Affordable Care Act, which amended the Public Health Service Act to create an abbreviated pathway to licensure for biosimilar agents. For biosimilars to be approved, Health Canada, the EMA, and the U.S. Food and Drug Administration (FDA), require that the quality, activity, safety and efficacy of the new agent be comparable to those of the original agent (Table I).

Since 2006, 25 biosimilar agents have been approved by regulatory agencies in Europe and North America (Table II). The first biosimilars were the somatropin analogs, introduced in Europe. Erythropoietin biosimilars followed in 2007, and agents similar to filgrastim, in 2008. It was not until more recently that agents similar to the monoclonal antibodies, which are larger and more complex biologics, were introduced. The first biosimilar was the anti–tumour necrosis factor α antibody infliximab, introduced in Europe in 2013. With the patents on several monoclonal antibodies now approaching or past expiry (including trastuzumab, bevacizumab, cetuximab, and rituximab), development programs for similar therapeutics are under way.

CURRENT LANDSCAPE AND CONSIDERATIONS FOR TRASTUZUMAB BIOSIMILARS

Trastuzumab (Herceptin) is a fully humanized monoclonal antibody to the extracellular domain IV of HER2, developed by Genentech (San Francisco, CA, U.S.A.). In the landmark trial by Slamon and colleagues[4], trastuzumab added to standard chemotherapy for metastatic disease significantly improved overall survival (OS) by approximately 5 months. Trastuzumab has since been shown to confer a survival benefit in multiple settings, including adjuvant and neoadjuvant treatment of HER2-positive (HER2+) breast cancer, and HER2+ metastatic gastric cancer[5–8]. Herceptin is now well-established in guidelines as a standard of care, but it remains costly: estimates place the cost at more than CA$4,500 per month or CA$54,000 for a full 1-year course of treatment[9,10].

The patent on Herceptin expired in 2014 in Europe, opening the door for biosimilar agents to enter the market and to lower the price by creating competition. In July 2017, a trastuzumab biosimilar agent, MYL-1410 (Mylan, Canonsburg, PA, U.S.A.), received unanimous recommendation for approval from the FDA's Oncologic Drugs Advisory Committee, and on 1 December 2017, it was approved. Despite that rapid progress, important regulatory and clinical factors have to be considered. Those factors include the sensitivity of the endpoints used to determine equivalence and safety, and extrapolation of indications, interchangeability, post-market surveillance, and naming.

TRASTUZUMAB BIOSIMILARS IN DEVELOPMENT

Early Disease

At the 2017 meeting of American Society of Clinical Oncology in Chicago, two phase III trials in early-stage breast cancer with trastuzumab biosimilars were presented (Table III). A phase III study involving 549 patients with stages I–IIIA HER2+ breast cancer evaluated CT-P6, the Celltrion Healthcare version of an anti-HER2 monoclonal antibody. The CT-P6 product was found to be noninferior in the rate of pathologic complete response (PCR), defined as the absence of invasive disease in the breast, and in the absence of invasive and *in situ* disease in the breast and axilla (ypT0/isypN0), with a risk ratio of 0.92[12]. Those findings met the predefined margin for risk. A second randomized phase III study with SB3, a trastuzumab biosimilar from Samsung Bioepis, demonstrated equivalence in neoadjuvant treatment, with a primary endpoint of PCR in the breast. The rate was 51.7% for SB3 compared with 42.0% for trastuzumab, for an adjusted ratio of 1.259 (95% confidence interval: 1.112 to 1.426)[15].

At the 2017 meeting of the European Society for Medical Oncology, studies on two additional agents in the neoadjuvant setting were presented. Pfizer's PF-05280014 was examined in the neoadjuvant setting in combination with docetaxel; pharmacokinetics was the primary endpoint, and PCR was a secondary endpoint. In this case, the biosimilar agent was noninferior, with a PCR of 47% compared with 50% for trastuzumab (see NCT02187744 at http://ClinicalTrials.gov). Amgen's ABP 980 also resulted in a noninferior PCR when combined with docetaxel in the neoadjuvant setting[14].

Metastatic Disease

An evaluation of CT-P6 was also conducted in metastatic HER2+ breast cancer (Table III). In a pooled analysis of data from phase I/IIB and III studies comparing CT-P6–paclitaxel with trastuzumab–paclitaxel for metastatic disease, the overall response rates (ORRS) during the first 8 cycles of treatment were 57% and 62% respectively (5% difference; 95% confidence interval: –0.14 to 0.04). That finding met the criteria for equivalence. Median time to progression was 11.07 months with CT-P6 and 12.52 months with trastuzumab, with serious adverse event rates of 13.5% and 12.1% respectively[11]. The full trial has yet to be published; however, in January 2014, CT-P6 was granted approval in South Korea for metastatic breast cancer (MBCA), early breast cancer (EBC), and gastric cancer. In the population with metastatic disease, Biocad's BCD-022 also demonstrated a noninferior ORR (primary endpoint) of 53.6% compared with 53.70% in the group receiving Herceptin–paclitaxel. Complete responses, partial responses, stable disease, and progression rates were also similar (Table III).

The Heritage study, a phase III study evaluating the biosimilar MYL-1401O combined with docetaxel in HER2+ MBCA, showed a noninferior ORR of 69.6% compared with 64% with Herceptin–docetaxel, meeting the endpoint of equivalence (hazard ratio: 1.09; 95% confidence interval: 0.954 to 1.237). Progression-free survival (PFS) events were similar in the two groups, at 21.1% and 17.8% respectively. The PFS results were updated at the 2017 international congress of the European Society for Medical Oncology, showing a hazard ratio for PFS of 0.96. The OS at 48 weeks was 89.1% (MYL-1401O) compared with 85.1% (Herceptin). Those results led to a recommendation from the Oncologic Drugs Advisory Committee to approve the agent in MBCA and EBC in addition to advanced gastric cancer. Also at the 2017 congress, PF-05280014 in combination with paclitaxel

TABLE I Characteristics of the European, American, and Canadian regulations concerning biosimilars

Characteristic	European Medicines Agency	U.S. Food and Drug Administration	Health Canada
Preclinical data			
In vitro	■ Concentration–activity levels, pharmacokinetics, pharmacodynamics data	■ Analytic studies demonstrating that the product is highly similar in structure and function (the more comprehensive the characterization, the more useful it will be in determining any requirement for further studies)	■ Receptor binding studies should be conducted, when appropriate
In vivo	■ Based on the need for further confirmation after *in vitro* studies; focus (one or more of pharmacokinetics, pharmacodynamics, or safety) depends on the need for additional information	■ Animal studies to include assessment of toxicity	■ Pharmacodynamics and pharmacokinetics studies; at least 1 repeat-dose toxicity study including toxicokinetic parameters
Clinical data			
Purpose	■ Pharmacokinetics, pharmacodynamics, and immunogenicity assessment; pharmacodynamics study might be sensitive enough on its own ■ Must also demonstrate safety and efficacy	■ Pharmacokinetics, pharmacodynamics, and immunogenicity assessment are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions	■ Pharmacokinetics, pharmacodynamics, clinical efficacy and safety assessment
Population	■ Sensitive to demonstrate equivalence	■ Sensitive to demonstrate equivalence	■ Population in whom product is indicated unless otherwise justified
Endpoint	■ For an anticancer monoclonal antibody, disease-free survival, progression-free survival, and overall survival are preferred	■ Endpoint sensitive to detect clinically meaningful difference ("totality of the evidence" approach)	■ Endpoint sensitive to detect clinically meaningful differences
Interchangeability	■ Substitution policies are within the remit of the E.U. member states	■ Possible; requires more complex pathway to approval, with less reliance on totality of evidence	■ Not recommended
Extrapolation of indications	■ Possible, based on the overall evidence of comparability provided from the comparability exercise and with adequate justification; if different mechanisms of action are relevant (or uncertainty exists), applicants should supply relevant data	■ Possible, based on scientific justification including mechanism of action, pharmacokinetics, and biodistribution in various patient populations, immunogenicity in various populations, and differences in toxicities expected	■ Possible; should be justified based on mechanism of action, pathophysiologic mechanism, safety profile in the respective conditions or populations (or both), and clinical experience with reference drug
Post-marketing surveillance or pharmacovigilance	■ Applicant should present risk-management plan in accordance with E.U. legislation and pharmacovigilance guidelines	■ Should take into account any safety or effectiveness concerns; should have mechanism to differentiate between events associated with the product and those with reference product (four-letter identification suffix known as "biologic modifier")	■ Adverse drug reaction reports and periodic safety update reports required ■ The authority to suspend an authorization is outlined in the Food and Drug Regulations ■ Products must be labelled indicating that the product is a "subsequent entry biologic" ■ There should be no claims that the biosimilar is better
Labelling	■ Summary of product characteristics must be derived from those of the reference product	■ Labels require "biosimilarity statement" describing the biosimilar product's relationship to its reference product ■ Comparative data demonstrating biosimilarity should not be included on the label	■ Statement indicating that the product is a biosimilar and that similarity between the drugs has been established ■ Comparative data generated by the biosimilar for which the decision for market authorization was made summarized in tabular format ■ Relevant safety and efficacy information from the biologic drug authorized in Canada to which a reference is made ■ There should be no claims for bioequivalence or clinical equivalence

in the first line for MBCA was shown, in a randomized double-blind study, to produce a similar response, with a risk ratio for ORR of 0.940 [95% confidence interval: 0.842 to 1.049 (within the pre-specified equivalence margin of 0.8 to 1.25)][13]. The 1-year PFS was 56% for PF-05280014 and 52% for trastuzumab. The 1-year survival was similar (88.84% vs. 87.96%). Safety was also similar in the two groups (Table III).

TABLE II Biosimilar agents currently approved in the European Union, the United States, and Canada

Reference drug	Biosimilars approved by ...					
	European Medicines Agency		U.S. Food and Drug Administration		Health Canada	
	Name	Date	Name	Date	Name	Date
Adalimumab	Solymbic[a]	2017				
	Amgevita[a]	2017				
Bevacizumab			ABP 215[a]	2017		
Enoxaparin sodium	Thorinane[b]	2016				
	Inhixa[c]	2016				
Epoetin alfa	Abseamed[d]	2007				
	Binocrit[e]	2007				
	Epoetin Alfa Hexal[f]	2006				
Epoetin zeta	Retacrit[g]	2007				
	Silapo[h]	2007				
Etanercept	Benepali[i]	2016			Brenzys[j]	2016
Filgrastim	Accofil Biograstim[k]	2008	Zarxio[l]	2015	Grastofil[m]	2015
	Filgrastim Hexal[f]	2009				
	Grastofil[m]	2013				
	Nivestim[g]	2010				
	Ratiograstim[n]	2008				
	Tevagrastim[o]	2008				
	Zarzio[e]	2009				
Follitropin alfa	Bemfola[p]					
	Ovaleap[o]	2013				
Infliximab	Flixabi[q]	2016	Inflectra[g]	2016	Inflectra[g]	2014
	Inflectra[g]	2013			Remsina[r]	2014
	Remsima[r]	2013				
Insulin glargine	Abasaglar[s]	2014	Basaglar[s]	2014	Basaglar[s]	2015
Somatropin	Omnitrope[e]	2006			Omnitrope[e]	2009

[a] Amgen, Thousand Oaks, CA, U.S.A.
[b] Pharmathen, Athens, Greece.
[c] Shenzhen Techdow Pharmaceutical, Shenzhen, P.R.C.
[d] Salmon Pharma, Basel, Switzerland.
[e] Novartis, Basel, Switzerland.
[f] Hexal, Holzkirchen, Germany.
[g] Hospira, Lake Forest, IL, U.S.A.
[h] Stada Arzneimittel, Bad Vilbel, Germany.
[i] Wyeth, Madison, NJ, U.S.A.
[j] Merck Sharp and Dohme, Kenilworth, NJ, U.S.A.
[k] Accord Healthcare, London, U.K.
[l] Sandoz, Holzkirchen, Germany.
[m] Apotex Technologies, Toronto, ON.
[n] Ratiopharm, Ulm, Germany.
[o] Teva Pharmaceutical Industries, Petah Tikva, Israel.
[p] Finox Biotech, Bergdorf, Switzerland.
[q] Biogen, Cambridge, MA, U.S.A.
[r] Celltrion Healthcare, Incheon, R.O.K.
[s] Eli Lilly and Company, Indianapolis, IN, U.S.A.

TABLE III Phase III studies evaluating trastuzumab biosimilars

Agent	Company	Phase	Indication	Trial status	Results	Drug status
CT-P6 (Herzuma)	Celltrion Healthcare (Incheon, R.O.K.)	Pooled I/IIB–III	First-line mBCa	Competed	For CT-P6 vs. Herceptin[a]: ORR: 57% vs. 62%; mTTP: 11.07 months vs. 12.52 months (Young-Hyuck *et al.,* 2013[11])	Available in South Korea
		III	Early BCa (NAT)	Completed	Noninferior pCR (ypT0/isypN0); 46.8% vs. 50.4% (CT-P6 vs. trastuzumab); risk ratio: 0.92 (Stebbing *et al.,* 2017[12])	
PF-05280014	Pfizer (New York, NY, U.S.A.)	III	mBCa	Active, not recruiting	Risk ratio ORR: 0.940 over trastuzumab; 1-year PFS: 56% vs. 52%; 1-year survival: 88.8% vs. 87.9% (Pegram et al., 2017[13])	
		III	Early BCa (NAT)	Completed	ABP-980 vs. Herceptin: Noninferior pCR: 47% vs. 50% (NCT02187744)	
ABP-980	Amgen (Thousand Oaks, CA, U.S.A.)	III	Early BCa (NAT)	Completed	Non-inferior pCR (results not posted) (Minckwitz *et al.,* 2017[14])	
SB3	Samsung Bioepis (Incheon, R.O.K.)	III	Early BCa (NAT)	Completed	SB3 vs. trastuzumab: equivalence in breast pCR: 51.7% vs. 42.0%; adjusted ratio: 1.259 (Pivot *et al.,* 2018[15])	
MYL-1410	Mylan (Canonsburg, PA, U.S.A.)	III	mBCa	Completed	MYL-1410 vs. Herceptin: noninferior ORR: 69.6% vs. 64% (HR: 1.09; 95% CI: 0.95 to 1.24); HR PFS: 0.96; OS at 48 weeks: 89.1% vs. 85.1% (Rugo et al., 2016[16])	Received approval from the U.S. Food and Drug Administration July 2017
BCD-022	Biocad (Saint Petersburg, Russia)	III	mBCa	Completed	BCD-022 vs. Herceptin: ORR: 53.6% vs. 53.7%; progression rate no different: 21.4% vs. 20.4%; (NCT01764022)	Received approval from Russian regulatory body January 2016.
CanMab	Biocon (Bengaluru, India)			NA	NA	Available in India (October 2013)
HD201	Hanwha Chemical (Seoul, R.O.K.)	III	mBCa	Not yet open		

[a] Genentech, San Francisco, CA, U.S.A.

mBCa = metastatic breast cancer; ORR = overall response rate; mTTP = median time to progression; BCa = breast cancer; ASCO = American Society of Clinical Oncology; NAT = neoadjuvant treatment; pCR = pathologic complete response; PFS = progression-free survival; ESMO = European Society for Medical Oncology; NA = not available.

REGULATORY CONSIDERATIONS IN BIOSIMILAR DEVELOPMENT

Comparability Trial Endpoint

When new cancer therapies are evaluated, OS has been considered the "gold standard," especially by regulatory authorities. In reality, survival endpoints might not be sensitive enough when considering comparability (such as in the case of biosimilar agents). It might also mean that the sample size required for adequate statistical inference would be prohibitively large.

In 2015, Jackisch *et al.*[17] evaluated the sensitivity of endpoints for both MBCA and EBC in similarity studies of trastuzumab and biosimilar agents. They used ORR and PFS data for MBCA and total PCR and event-free survival (EFS) in the neoadjuvant setting reported in a meta-analysis of data from trastuzumab clinical trials. Despite prior findings suggesting tumour response as a potential surrogate for PFS in MBCA[18], they found that using the shorter-term endpoint of ORR to measure equivalence could lead to substantial differences in long-term PFS. At an equivalence margin of 10% for ORR, a difference in PFS of close to 3.2 months could be observed. For equivalence margins of 15%, the difference in PFS could be more than 4 months. For a stricter margin of 5% for ORR, the sample size required to correlate with PFS would be close to 4000 patients. As with ORR and PFS, total PCR and EFS have been shown to correlate, at least in the HER2+ subgroup[19]. Again, based on a meta-analysis of clinical trials, Jackrisch *et al.*[17] calculated that a 10% equivalence margin in total PCR corresponded with a difference of 3.8% in 3-year EFS; for a 15% equivalence margin, the predicted loss in 3-year EFS was 6.8%.

Extrapolation of Indications

Based on the results of phase III clinical trials, trastuzumab is currently indicated in the treatment of HER2+ MBCA, EBC, and metastatic gastric cancer. "Extrapolation of indications" allows an agent to be used for the treatment of certain conditions or in populations in which it has not been directly studied, based on evidence of similarity in another condition or population. For example, if an agent were to be shown to be similar to trastuzumab in MBCA, extrapolation of indications would allow that agent to be used in EBC or gastric cancer.

Regulatory bodies have made recommendations about indication extrapolation for biosimilars (Table I). A common requirement is that relevant mechanisms of action should be the same for the reference drug and for the biosimilar agent. For trastuzumab, multiple mechanisms of action are proposed as being important for effectiveness, including HER2 degradation, antibody-dependent cellular cytotoxicity, and interference in downstream signalling[20]. The relative contribution of each mechanism to the treatment of various populations or various cancers is unknown, and each might be disproportionately affected in biosimilars by production differences and post-translational modifications.

Beyond mechanistic uncertainty, other factors might limit clinical similarity in various indications. Minor differences in drug products can affect immunogenicity, and those differences are essentially impossible to exclude without clinical trials. To support indication extrapolation, it is therefore recommended by the FDA that immunogenicity be investigated in the patient population that carries the highest risk of an immune response and immune-related adverse events. Similarly, the EMA suggests that clinical trials be carried out in a sufficiently sensitive and homogeneous population. Most MBCA patients have already been exposed to treatment with chemotherapy, radiotherapy, or both, which have known immunosuppressive effects[21]. As a result, compared with women affected by EBC, women affected by MBCA are more likely to have some degree of immunologic impairment, making MBCA patients a less-sensitive population for comparisons of biosimilars in clinical trials. Moreover, patients with metastatic disease are a heterogeneous group, with variation in prior treatment exposure, line of therapy, disease burden, comorbidities, and location of metastases. Given those issues, it would be reasonable to consider extrapolation from the neoadjuvant or adjuvant setting to metastatic disease; the reverse, however, would be uncertain.

Extrapolation of indications can also lead to extrapolation to various combinations of drugs in which the biosimilar agent has not been directly tested. The MYL-1401O study (Table III) looked at the biosimilar agent in combination with docetaxel in the first line for metastatic disease, because that combination was the standard of care established by Slamon *et al.*[16] in 2001. Since that time, however, the combination of taxane chemotherapy and trastuzumab with pertuzumab, a second HER2-targeted antibody, has been associated with increased OS and is now established as the standard of care in the first line for MBCA. Whether the equivalence demonstrated in the Heritage study is representative of the combination with pertuzumab is uncertain.

Interchangeability and Exchange

"Interchangeability" implies that two medical treatments have an identical therapeutic effect, such that patients can be safely switched from one to the other. Despite trials to ensure that biosimilars are therapeutically equivalent, it might not be safe for patients already maintained on a biologic agent to be switched over to a biosimilar, and vice versa. Minor differences in structure have the potential to result in a serious immunologic effect. For that reason, data showing the safety and efficacy of switching from the reference drug to the biosimilar agent must be presented before the two agents are considered interchangeable.

In the United States, the FDA has two pathways for licensing biosimilar products. One is relatively simple and is used for agents that will not be deemed interchangeable; interchangeability requires the other, more complex path. In Europe, the interchangeability designation is determined by each individual country; currently, no consistent definition has been established. Without adequate interchangeability evidence, biosimilars are usually prescribed only to patients who have not previously been treated with the reference drug. That limitation on prescribing can restrict the degree to which the biosimilar can competitively affect the price of the reference drug.

Pharmacovigilance and Safety Monitoring

As is the case with most biologics, clinical testing before the approval of a biosimilar might not identify all possible associated adverse events. Evaluation of clinical safety for biosimilars should therefore continue after marketing begins[22]. All manufacturers of biologics, including those manufacturing biosimilars, must submit pharmacovigilance plans as part of the marketing authorization application[22]. The plan includes pre- and post-authorization immunogenicity testing, a risk management plan based on safety issues identified during the clinical trials, and post-marketing safety commitments such as targeted questionnaires, phase IV studies, and specialized follow-up for long-term use[23,24].

The goal of a pharmacovigilance plan is to identify and understand the frequency and nature of product-associated adverse events that might not have been observed during clinical testing, and to provide a framework to rapidly report and manage such incidences[24,25]. Given that the full scope of trastuzumab's mechanisms of action remains largely unknown, post-authorization immunogenicity testing is of particular importance for the pharmacovigilance plan of trastuzumab biosimilars[26]. Subsequent immunogenicity events can range from inconsequential non-neutralizing antibodies to more severe toxicities, including loss of efficacy and build-up of true resistance to the reference product. The potential effects on both efficacy and safety render the immunogenicity of a trastuzumab biosimilar a critical feature that must be carefully monitored in post-marketing settings[26]. The EMA, FDA, and Health Canada have guidelines for post-marketing surveillance of biosimilars (Table I).

Central to all pharmacovigilance plans is the need to be able to accurately trace the medicine given to a patient, which makes labelling of the product is important[27]. In the United States in 2014, the FDA issued updated regulations for labelling, including detailed recommendations for the labelling of biosimilar products. Health Canada also updated their guidelines to include recommendations on labelling. Health Canada recommends including a table containing information about the comparability testing, but the FDA intentionally suggests excluding such a table on the grounds that it might be confusing or potentially misleading (Table I). The EMA has taken a different approach, recommending that, as with generic drugs, biosimilars should derive the summary of product characteristics for the label from the reference product. That recommendation has been criticized for not highlighting the differences between biosimilars and reference products.

THE VALUE OF BIOSIMILARS

Much of the value proposition for biosimilars consists of the potential for a substantial cost reduction, based on previous experience with generic small-molecule compound drugs[28]. However, given the considerations discussed here, the manufacturing of biosimilars clearly requires a more extensive and lengthier clinical testing program[29].

The research and development costs of biosimilars are many times those for developing and manufacturing small-molecule generics[30]. For example, in the United States, estimates suggest that bringing a biosimilar to market will cost between $10 million and $40 million and will take 6–9 years; for generics, the expected cost is $1–$2 million, with a 3-year timeline[31]. Biosimilars are therefore likely to be marketed only at a 20%–30% discount compared with the cost of the original products; generics are generally sold at about a 75% discount[31]. Preferential formulary placement for the biosimilar would require a discount of 20%–50% compared with the originator biologic[32].

In addition, few drug manufacturers have the complex research and development capabilities to advance a biosimilar to market. It is therefore unlikely that the competition dynamics for biosimilars will echo those of the small-molecule drug market[33]. In the absence of a significant discount, preference in the short-term might be given to the reference biologic[32]. Although it is not the intention of similarity exercises, a biosimilar agent might prove to be more effective than the reference drug—for example, when the Samsung Bioepis and Mylan products demonstrated higher PCR rates in comparisons with trastuzumab (Table I). Such a situation could open the door to further increased pricing.

Because branded biologic agents are generally associated with high cost, the value of biosimilars to the health care system might be inversely associated with the accessibility and affordability of branded biologic agents[32]. In countries in which branded biologic agents are traditionally available, patients and physicians alike might question the justification of administering a biosimilar solely to lower costs[32]. The lack of education for many stakeholders involved in the biosimilar decision-making process could further limit the perceived value of biosimilars and their integration into clinical practice[34]. Many key parties in countries in which branded biologic agents are available and accessible might be unfamiliar with biosimilars: how they differ from generics and interchangeable biologic drugs, whether the differences are or are not important, and how to manage any perceived risk that might be associated with biosimilars[34].

In the long term, predictability and clarity in the regulatory requirements and market for biosimilars could encourage greater participation of diverse stakeholders worldwide in biosimilar development and could support more price competition[32]. By 2020, more than US$67 billion of total global sales of biologic therapies will be coming off-patent in the United States and the European Union[28]. Even with a discount as low as 20% from biosimilars, the projected savings in the United States are substantial, ranging from US$3 billion to US$4.5 billion annually, and up to US$378 billion over the next two decades[31]. An annual savings of €1.6 billion has been predicted for Europe if biosimilars to 5 patent-expired biologic drugs are successfully developed[30]. Because of escalating health care costs, biosimilars show great promise for enhancing access to necessary medications for larger audiences, while containing payer costs in various disease states[35].

CONCLUSIONS

Biosimilar agents are being developed at a rapid pace and will play an important role in cancer treatment. The aim of clinical trials with biosimilars is to demonstrate

clinical equivalence. Regulatory guidelines for biosimilar antibodies exist, but questions about how best to assess equivalence and to integrate those agents into clinical practice remain. Introducing them into the standard of care will be a dynamic process involving multiple stakeholders, but could potentially help to control the cost of cancer care. Whether biosimilar agents will be the sole option available, or whether the choice of the reference biologic will be available, remains to be seen. Education for physicians about these complex issues will be imperative.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SV sits on advisory boards for Roche, Pfizer, Novartis, Eli Lilly, Merck, and Amgen. The remaining authors have no relevant conflicts to disclose.

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REFERENCES

1. Bazargani YT, de Boer A, Schellens JH, Leufkens HG, Mantel-Teeuwisse AK. Essential medicines for breast cancer in low and middle income countries. *BMC Cancer* 2015;15:591.
2. Camacho LH, Frost CP, Abella E, Morrow PK, Whittaker S. Biosimilars 101: considerations for U.S. oncologists in clinical practice. *Cancer Med* 2014;3:889–99.
3. Health Canada, Health Products and Food Branch. *Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs.* Ottawa, ON: Health Canada; 2016.
4. Slamon DJ, Leyland-Jones B, Shak S, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783–92.
5. Bang YJ, Van Cutsem E, Feyereislova A, *et al.* Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (TOGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;376:687–97.
6. Gianni L, Pienkowski T, Im YH, *et al.* Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012;13:25–32.
7. Slamon D, Eiermann W, Robert N, *et al.* on behalf of the Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;365:1273–83.
8. Perez EA, Romond EH. Suman VG, *et al.* Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2–positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol* 2014;32:3744–52.
9. Goldenberg MM. Pharmaceutical approval update. *P T* 2012;37:499–502. [Erratum in: *P T* 2012;37:600]
10. Drucker A, Skedgel C, Virik K, Rayson D, Sellon M, Younis T. The cost burden of trastuzumab and bevacizumab therapy for solid tumours in Canada. *Curr Oncol* 2008;15:136–42.
11. Young-Hyuck I, Odarchenko P, Grecea D, *et al.* Double-blind, randomized, parallel group, phase III study to demonstrate equivalent efficacy and comparable safety of CT-P6 and trastuzumab, both in combination with paclitaxel, in patients with metastatic breast cancer (MBC) as first-line treatment [abstract 629]. *J Clin Oncol* 2013;31:. [Available online at: https://meetinglibrary.asco.org/record/85469/abstract; cited 23 March 2018]
12. Stebbing J, Baranau YV, Baryash V, *et al.* Double-blind, randomized phase III study to compare the efficacy and safety of CT-P6, trastuzumab biosimilar candidate versus trastuzumab as neoadjuvant treatment in HER2 positive early breast cancer (EBC) [abstract 510]. *J Clin Oncol* 2017;35:. [Available online at: https://meetinglibrary.asco.org/record/145550/abstract; cited 23 March 2018]
13. Pegram M, Tan-Chiu E, Freyman A, *et al.* A randomized, double-blind study of PF-05280014 (a potential trastuzumab biosimilar) vs trastuzumab, both in combination with paclitaxel, as first-line treatment for HER2-positive metastatic breast cancer [abstract 238PD]. *Ann Oncol* 2017;28(suppl 5):. [Available online at: https://academic.oup.com/annonc/article/28/suppl_5/mdx365.001a/4108467; cited 23 March 2018]
14. von Minckwitz G, Ponomarova O, Morales S, Zhang N, Hanes V. Efficacy and safety of biosimilar ABP 980 compared with trastuzumab in HER2 positive early breast cancer [abstract 151PD]. *Ann Oncol* 2017;28(suppl 5):. [Available online at: https://academic.oup.com/annonc/article/28/suppl_5/mdx362.002/4108319; cited 23 March 2018]
15. Pivot X, Bondarenko I, Nowecki Z, *et al.* Phase III, randomized, double-blind study comparing the efficacy, safety, and immunogenicity of SB3 (trastuzumab biosimilar) and reference trastuzumab in patients treated with neoadjuvant therapy for human epidermal growth factor receptor 2-positive early breast cancer. *J Clin Oncol* 2018;:[Epub ahead of print].
16. Rugo HS, Barve A, Waller CF, *et al.* Heritage Study: a randomized double blind phase III safety and efficacy trial of the proposed trastuzumab biosimilar MYL-1401O vs Herceptin [abstract LBA503]. *J Clin Oncol* 2016;34:. [Available online at: https://meetinglibrary.asco.org/record/124302/abstract; cited 23 March 2018]
17. Jackisch C, Scappaticci FA, Heinzmann D, *et al.* Neoadjuvant breast cancer treatment as a sensitive setting for trastuzumab biosimilar development and extrapolation. *Future Oncol* 2015;11:61–71.
18. Burzykowski T, Buyse M, Piccart-Gebhart MJ, *et al.* Evaluation of tumor response, disease control, progression-free survival, and time to progression as potential surrogate end points in metastatic breast cancer. *J Clin Oncol* 2008;26:1987–92.
19. Cortazar P, Zhang L, Untch M, *et al.* Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014;384:164–72.
20. Vu T, Claret FX. Trastuzumab: updated mechanisms of action and resistance in breast cancer. *Front Oncol* 2012;2:62.
21. Tsavaris N, Kosmas C, Vadiaka M, Kanelopoulos P, Boulamatsis D. Immune changes in patients with advanced breast cancer undergoing chemotherapy with taxanes. *Br J Cancer* 2002;87:21–7.
22. Rak Tkaczuk KH, Jacobs IA. Biosimilars in oncology: from development to clinical practice. *Semin Oncol* 2014;41(suppl 3):S3–12.
23. European Union, European Medicines Agency (EMA), Committee for Medicinal Products for Human Use. *Guideline on Immunogenicity Assessment of Monoclonal Antibodies Intended for* In Vivo *Clinical Use.* London, UK: EMA; 2012.
24. European Union, European Medicines Agency (EMA), Heads of Medicines Agencies. *Guideline on Good Pharmacovigilance Practices (GVP): Module V—Risk Management Systems.* London, UK: EMA; 2012.

25. United States, Department of Health and Human Services, Food and Drug Administration (FDA). *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*. Silver Spring, MD: FDA; 2005. [Available online at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071696.pdf; cited 21 February 2018]
26. Pivot X, Aulagner G, Blay KY, *et al.* Challenges in the implementation of trastuzumab biosimilars: an expert panel's recommendations. *Anticancer Drugs* 2015;26:1009–16.
27. Cortés J, Curigliano G, Diéras V. Expert perspectives on biosimilar monoclonal antibodies in breast cancer. *Breast Cancer Res Treat* 2014;144:233–9.
28. Henry D, Taylor C. Pharmacoeconomics of cancer therapies: considerations with the introduction of biosimilars. *Semin Oncol* 2014;41;(suppl 3):S13–20.
29. Weise M, Bielsky MC, De Smet K, *et al.* Biosimilars: what clinicians should know. *Blood* 2012;120:5111–17.
30. Cornes P. The economic pressures for biosimilar drug use in cancer medicine. *Target Oncol* 2012;7(suppl 1):S57–67.
31. Helwick C. Economic implications of biosimilars in oncology. *Value Based Cancer Care* 2011;2:. [Available online at: http://www.valuebasedmyeloma.com/vbcc-issues/2011/december-2011-vol-2-no-7/1196-vbcc-1196; cited 6 February 2018]
32. Rompas S, Goss T, Amanuel S, *et al.* Demonstrating value for biosimilars: a conceptual framework. *Am Health Drug Benefits* 2015;8:129–39.
33. Blackstone EA, Joseph PF. The economics of biosimilars. *Am Health Drug Benefits* 2013;6:469–78.
34. Zelenetz AD, Ahmed I, Braud EL, *et al.* NCCN biosimilars white paper: regulatory, scientific, and patient safety perspectives. *J Natl Compr Canc Netw* 2011;9(suppl 4):S1–22.
35. Lammers P, Criscitello C, Curigliano G, Jacobs I. Barriers to the use of trastuzumab for HER2+ breast cancer and the potential impact of biosimilars: a physician survey in the United States and emerging markets. *Pharmaceuticals (Basel)* 2014;7:943–53.