

Opportunities and Challenges in Biosimilar Uptake in Oncology

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Since 2015, when the FDA approved the first biosimilar under the Biologics Price Competition and Innovation Act of 2009, 9 additional biosimilars have received agency approval, including 3 with an oncology indication.¹ Although tbo-filgrastim was approved under the traditional drug approval pathway, many viewed this approval as an example of what biosimilars would look like in the United States following the first approved biosimilar in the European Union. By January 2018, at least 60 biosimilars were enrolled in the FDA's biosimilar development program, with FDA commissioner Scott Gottlieb, MD, reporting that the agency had received requests for meetings to discuss biosimilars for 27 distinct reference biologics.²

Most recently, pegfilgrastim-jmdb was approved by the FDA to decrease the incidence of infection with febrile neutropenia in patients receiving myelosuppressive chemotherapy similar to its reference product. Bevacizumab-awwb, for the treatment of adult patients with certain colorectal, lung, brain, kidney, and cervical cancers; and trastuzumab-dkst, for the treatment of certain breast and stomach cancers, are approved biosimilars that will have the greatest impact in the oncology arena. The expected lower costs of these drugs are likely to increase access to these therapies, which are among the most expensive drugs in the United States and are often out of reach for the patients who need them most.³⁻⁵

The successful uptake of biosimilars in the practice of oncology, however, rests on numerous factors, involving clinicians, patients, payers, legislators, and manufacturers. These include the number and timing of entrants into the market; patient and provider acceptability; development costs; competition and litigation involving reference product manufacturers; market size and share; pricing; payer coverage and utilization policies; cost sharing; and regulatory policies around interchangeability (Figure 1).^{6,7}

Clinician and Patient Uptake of Biosimilars in Oncology

The most important and influential stakeholders for biosimilar acceptance and usage are physicians and patients. However, there is evidence of significant gaps in knowledge for both audiences.

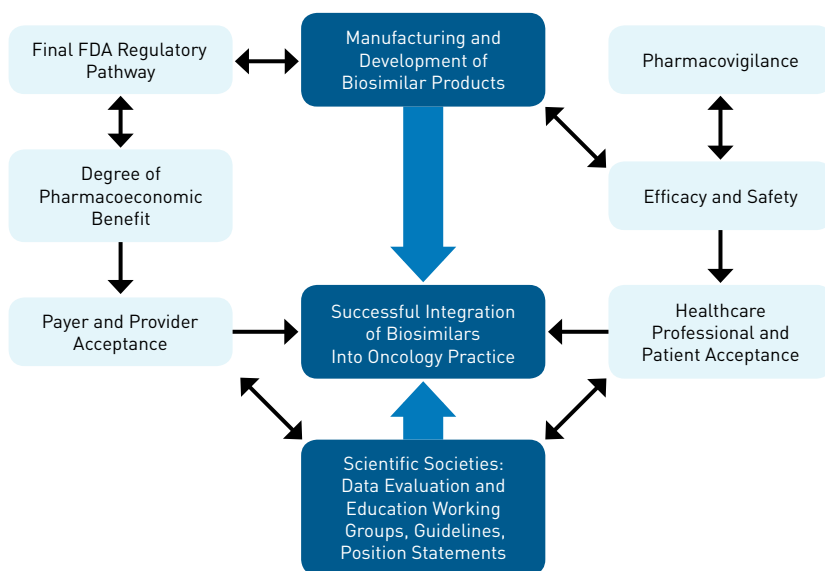
ABSTRACT

There are now 10 approved biosimilars in the United States, including 3 oncology drugs, and at least 16 others in late-stage development. The introduction of competition into the biologic space launches a new era in the treatment of cancer, possibly increasing access to the extremely costly biologics. The most important and influential stakeholders for biosimilar acceptance and usage are healthcare providers, such as pharmacists and physicians, as well as patients. Gaining their support requires extensive education, postmarketing pharmacovigilance, resolving concerns about immunogenicity, and allowing interchangeability and substitution. Patients require education on the basic definition of biosimilars versus generic drugs, how biosimilars are tested and approved, costs, and availability of clinical trials. Meanwhile, payers may need to find ways to incentivize physicians to prescribe biosimilars over biologics, as well as to provide information on cost and quality directly to patients in order to drive uptake. Finally, legal challenges to approved and pending biosimilars have limited the market access of these agents.

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FIGURE 1. Parameters Influencing the Successful Uptake and Integration of Biosimilars Into US Oncology Practices⁷



Recreated from *Seminars in Oncology*, vol 41, suppl 3. Rak Tkaczuk KH, Jacobs IA. Biosimilars in oncology: from development to clinical practice, pages S3-S12, Copyright 2014, with permission from Elsevier.

Physician Barriers

A survey of 376 US oncologists (part of a larger survey that included 1245 oncologists total from the United States, Europe, and Latin America) found that they lacked technical knowledge and understanding of the effects of biologics and biosimilars sharing the same nonproprietary name, and misunderstanding if biologics and biosimilars are structurally and therapeutically identical.⁸ Earlier surveys also found significant knowledge gaps regarding all aspects of biosimilars (chemical structure, difference from reference product, approval process, availability of biosimilars in the United States, etc) among clinicians of various specialties.⁹⁻¹²

Gaining physician support for and confidence in biosimilars will require evidence demonstrating that the biosimilar provides similar efficacy and safety to the reference product. Still, some aspects of the biosimilar concept remain unclear to practitioners surrounding the biosimilar approval process, required clinical trials, and pharmacovigilance. A 2018 statement by the American Society of Clinical Oncology (ASCO) on the appropriate use of biosimilars in clinical practice highlighted the need for postmarketing evidence development to enhance physician and patient confidence in their use. The authors noted that this was particularly important because regulatory review of biosimilars relies less on clinical data and more on structural, functional, and pharmacologic data. ASCO also noted the challenges of such postmarketing evidence, given the fragmentation of the US healthcare system. It suggested that its CancerLinQ database, which provides data on millions of de-identified patients, and

the pending FDA surveillance system, Sentinel, designed to monitor safety issues in clinical trials, could be used to collect these data.¹³

As with any biologic, physicians also have concerns about immunogenicity. Given that biosimilars will, by necessity, be manufactured in a slightly different manner from their reference product, there is concern that switching patients from a biologic to a biosimilar, or vice versa, could result in hypersensitivity reactions. To evaluate that possibility, some clinical trials have included product switching, although assessing immunogenicity often depends on the molecule and the indications studied.¹⁴

An important issue affecting physician uptake of biosimilars is interchangeability and substitution. To receive interchangeability designation, the manufacturer must demonstrate not only that the biosimilar has similar efficacy and safety to the biologic, but also that there is no greater risk in switching between the biologic and biosimilar than remaining on the reference product.¹⁵ The advantage to the

manufacturer is some level of exclusivity.¹⁶ The FDA announced a pathway to interchangeability in January 2017 and is expected to designate the first interchangeable products within the next 2 years.¹⁷

An interchangeability designation allows the biosimilar to be substituted for the reference product at the pharmacy level similar to the way generic products are substituted for brand drugs today. The physician can still reserve the right to designate the drug by name. Substitution, however, is controlled at the state level. By March 2018, nearly all states, the District of Columbia, and Puerto Rico had passed some type of legislation allowing substitution of biosimilars, although the details vary by state.¹⁸

The aforementioned survey of 376 US oncologists found that 80% believed it is critically or very important that they be notified if a biosimilar is substituted for the prescribed reference drug. They were also more likely than their Latin American or European peers to believe that patients could switch biologics mid-treatment and expect the same results.⁸

Early experience with the filgrastim biosimilar showed that providers were slower to incorporate biosimilars into their practice until they gained experience and felt comfortable prescribing the biosimilar. One health plan in the United States reported that 30% of filgrastim prescriptions were for the biosimilar, while another reported that prescriptions for the biologic had dropped by a third since the biosimilars entered the market, disclosing initial hesitation from oncologists to prescribe them. Today, many payers are beginning to give biosimilars preferred status on their formularies.¹⁹

Oncologists also tend to be more comfortable with trying new therapies for patients and adding newly approved drugs to their armamentarium fairly quickly. Moreover, practitioners are feeling pressure from patients about high-cost biologic therapies, causing many physicians to speak out about the cost of therapies.²⁰

Patient Knowledge Gaps

Patients need to understand the concept of biosimilars and their place in the treatment continuum. To accomplish this level of awareness requires education, so patients can make an informed decision on their care. A 2015 American Autoimmune-Related Diseases Association survey of 362 of its members, 96% of whom have an autoimmune disease, found that more than 80% did not know what biosimilar medicines were, while about half understood the difference between biologics and biosimilars.²¹

In another consumer-focused survey from the consulting firm PricewaterhouseCoopers conducted in 2015, 67% of consumers did not know what a biosimilar was, while just 17% chose the correct definition from several choices.²²

Patients require education on the basic definition of biosimilars versus generic drugs; how they are tested and approved; costs; and availability of clinical trials.¹⁴ The ASCO recommendations call for healthcare professionals to educate patients, and for medical societies, government sources, and patient advocacy organizations to provide public awareness and education programs, as well as use standardized, publicly available materials.¹³

Payers may also target patients directly with information about lower costs for biosimilars compared with the biologic medication. Medicare patients today pay a 20% co-payment for Part B drugs, which can be a significant cost for the higher priced biologics.²³ In addition, a growing percentage of commercially insured individuals have high-deductible health plans.²⁴ Thus, patients are becoming more aware of the cost of their healthcare.²⁵⁻²⁷

Payers and Reimbursement

The majority of cancer biologics are administered in an outpatient setting and paid for under the medical rather than pharmacy benefit (Part B for Medicare). Medicare typically reimburses for medication administered in a physician office or infusion clinic at a rate of the average sales price (ASP) plus 6% as an administrative fee.²⁸ To incentivize the prescribing of biosimilars, CMS set the administrative fee for the biosimilar based on the ASP of the reference product plus 6% of the reference product's ASP. How individual states will handle reimbursement under their Medicaid programs remains to be seen.²⁹ Moreover, in January 2018, CMS finalized a ruling on the hospital outpatient prospective payment system (OPPS) for 340b hospitals, adjusting reimbursement to ASP minus 22.5%.³⁰ This may impact the utilization of biosimilars in the ambulatory setting.

In the acute-care setting, biosimilars can be incorporated through the pharmacy and therapeutics (P&T) committee within the institution. This committee is primarily responsible for approving the pharmacy formulary system for the hospital and includes pharmacists, physicians, hospital administrators, nurses, and additional staff who support the medication use process. Many factors are taken into consideration when reviewing a drug to be placed on the formulary, including clinical effectiveness, operational objectives, cost, and product supply chain. Policies and procedures are approved that can include automatic substitution for medications to match the hospital formulary. Furthermore, the P&T committee can assist and direct staff educational programs that reflect changes to the formulary.

Additional payer reimbursement and requirements may also affect biosimilar uptake. Germany, which has one of the strongest uptakes of biosimilars in the world, incentivizes its doctors to prescribe biosimilars through quotas, budgeting, and monitoring programs, while key opinion leaders and medical associations provide education and integrate the use of biosimilars into their guidelines.³⁰ Providing similar incentives for clinicians could drive uptake in the United States and, with the movement toward value-based reimbursement, may help drive the utilization of biosimilars. For instance, payers could offer higher in-office payments for clinicians who meet certain prescribing levels for biosimilars versus biologics.²⁵

Another potential barrier to the clinical integration of biosimilars may be the temporal and financial investment required to make the distribution change from the current biologic to a biosimilar. It is important to take into consideration the fine details that participants in the supply chain, such as manufacturers, pharmacy benefit managers, and specialty pharmacies, have in place to encourage continued prescribing of the reference product.¹⁴

Finally, although there are now 10 approved biosimilar drugs, only 3 are currently on the market. These delays in launching the biosimilar products are a result of pending litigation from the reference drug manufacturer. This presents a challenge for the ability of the biosimilars to penetrate the market in a timely fashion. Furthermore, brand suppliers are bringing new products to the market by enhancing the original biologic, otherwise known as follow-on biologics or "biobetters."³¹ These new molecular entities are altered versions of approved biologics designed to improve their method of administration, safety, efficacy, or manufacturing.³² All of these issues may limit the potential cost savings from biosimilar use in the next several years, although their use will likely increase over time due to supply and demand factors.³³

The Economic Implications of Biosimilars in Cancer Therapy

Historically, when a generic drug enters the market, the cost is less than that of the brand manufacturer. However, payers should not

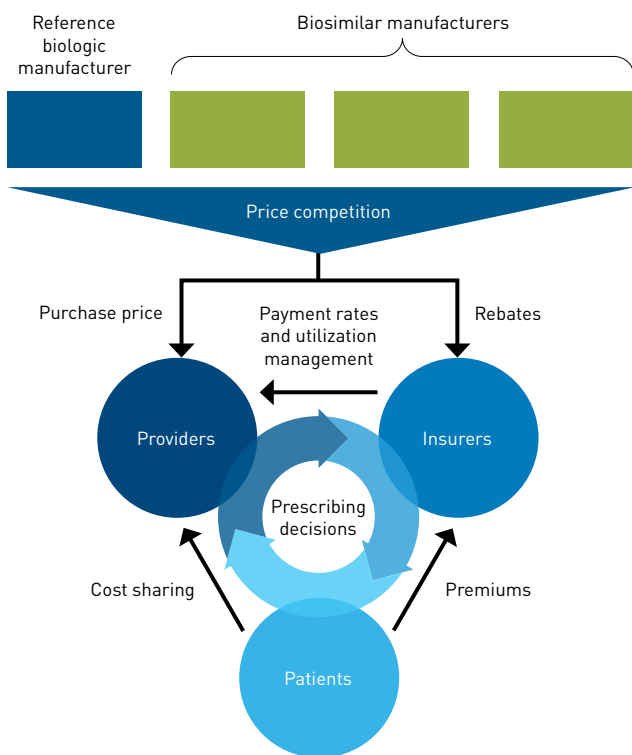
FIGURE 2. Biologic Market Relationships⁶

Figure adapted from Mulcahy AW, Hlávka JP, Case SR. *Biosimilar Cost Savings in the United States: Initial Experience and Future Potential*. Santa Monica, CA: RAND Corporation; 2017. www.rand.org/pubs/perspectives/PE264.html.

expect this level of price differential when it comes to biologics and biosimilars, nor even the 50% price differential they had hoped for.³¹ There are several reasons for this, including the higher cost of bringing a biosimilar to market. This can cost more than \$100 million and take 5 years or more compared with the \$2 million to \$5 million and 2 years required for a generic.³³

Other barriers to lower pricing include complex, high-cost manufacturing processes; direct marketing to clinicians to share clinical data and highlight the efficacy and safety of the biosimilar compared with the original drug; development of a sales force in a new therapeutic arena; the need for phase 4 studies to demonstrate real-world safety and efficacy; and the likelihood that there may be a limited number of biosimilars in a given category.³⁴

At the same time, rebates provided by pharmacy benefit managers and manufacturers that are tied to utilization of the reference drug may also mitigate any price reductions. Missing out on those rebates if patients are switched to biosimilars could make the reference drug much costlier, wiping out any savings from the biosimilar.³¹

A 2017 analysis from the RAND Corporation estimated that biosimilars would reduce direct spending on biologic drugs by \$54 billion between 2017 and 2026, or about 3% of the total estimated

biologic spending over the same period, with a range of \$24 billion to \$150 billion. The researchers cautioned, however, that the actual savings are dependent on industry, regulatory, prescriber, and insurer decisions, as well as potential future policy changes to strengthen the biosimilar market (Figure 2).⁶

As part of its analysis, RAND provided a case study on the uptake and cost savings of filgrastim-sndz and tbo-filgrastim. By the end of 2016, these 2 biosimilar-related products held a third of the total filgrastim market and were marketed at a 30% (tbo-filgrastim) and 45% (filgrastim-sndz) discount. RAND also noted that total spending on all 3 products (including filgrastim reference drug) dropped significantly between 2013 and 2016, suggesting the impact of the biosimilars. In addition, while the net price of filgrastim did not change during this time, both biosimilar-related drugs experienced large price decreases following their launch, likely due to competition in the marketplace, demonstrating that biosimilars could also increase access to more expensive drugs.^{6,35,36}

A 2017 simulation analysis of the cost savings resulting from the use of filgrastim-sndz versus filgrastim on 20,000 patients with follicular lymphoma found a per-cycle cost savings between \$327 and \$915, depending on the length of the cycle, yielding a savings between \$6.54 million (5-day cycle) and \$18.3 million (14-day cycle). The authors estimated that the savings would generate expanded access to the biologic obinutuzumab, approved for relapsed/refractory follicular lymphoma and previously untreated chronic lymphocytic leukemia, to between 60 and 169 patients in a budget-neutral manner.³⁷

The same analysis showed that switching patients from pegfilgrastim to filgrastim-sndz yielded savings of between \$55.9 million for 5 days of treatment and \$16.7 million for a 14-day cycle. The savings would expand access to obinutuzumab treatment for patients in a budget-neutral manner.³⁷

New and Emerging Cancer Biosimilar Agents

Several oncologic biosimilars to trastuzumab, rituximab, cetuximab, and bevacizumab are in late-stage clinical trials (Table 38-51).

Trastuzumab. The trastuzumab biosimilar CT-P6 demonstrated similar efficacy and safety in a head-to-head trial with trastuzumab (both combined with paclitaxel) in HER2-positive metastatic breast cancer (MBC) as well as in the neoadjuvant setting in women with early-stage breast cancer.^{38,39} The biosimilar BCD-022 also demonstrated similar efficacy and safety in the MBC setting.⁴⁰ Another trastuzumab biosimilar candidate, SB3, was also studied in the neoadjuvant study in patients with early-stage breast cancer. It demonstrated equivalence based on pathologic clinical response rate, safety, pharmacokinetics, and immunogenicity.⁴¹

Rituximab. Several biosimilars are under investigation for rituximab, including CT-P10 in patients with follicular lymphoma. Early results from an ongoing randomized clinical trial in patients with late-stage disease demonstrated CT-P10's similar efficacy, safety,

TABLE. Investigational Oncology Biosimilars³⁸⁻⁵¹

Biosimilar	Clinical Trial	Outcome
Trastuzumab		
CT-P6	Phase 3 in 475 patients with HER2-positive MBC	Similar ORR and TTP in combination with paclitaxel
	Phase 3 in neoadjuvant setting in 549 women with early-stage breast cancer in conjunction with neoadjuvant docetaxel and FEC	Similar PCR and safety between the 2 cohorts
BCD-022	Phase 3 in 46 patients with HER2-positive MBC randomized to BCD-022 or trastuzumab, both with paclitaxel	Noninferiority to trastuzumab with similar safety, tolerability, and immunogenicity
SB3	Phase 3 in 800 HER2-positive patients in the neoadjuvant setting who also received docetaxel and FEC	Equivalence by ratio of breast PCR rates; similar safety, pharmacokinetics, and immunogenicity
HLX02	Untreated MBC	Ongoing
CT-P10	Phase 3 in 140 patients with newly diagnosed, advanced-stage follicular lymphoma	No significant differences in efficacy, pharmacokinetics, or safety. Application pending with the FDA
BCD-020	Phase 3 in 92 patients with non-Hodgkin lymphoma	Similar ORR and adverse event profile between both arms
HLX01	Phase 3 study in combination with CHOP in previously untreated patients with CD20+ DLBCL	Ongoing
GP2013	Phase 3 study in 629 patients with previously untreated advanced follicular lymphoma (both arms also received cyclophosphamide, vincristine, and prednisone)	Demonstrated equivalence in ORR with similarity for efficacy and for PK and PD parameters. Application pending with FDA
Rituximab		
HD201	Phase 3 in patients with MBC	Ongoing
Bevacizumab		
BCD-021	Phase 3 in 138 patients with nonsquamous NSCLC in combination with carboplatin plus paclitaxel	Demonstrated similar ORR, safety, and immunogenicity
SB8	Phase 3 in patients with advanced nonsquamous NSCLC	Ongoing
MB02	Phase 3 in patients with stage IIIB/IV NSCLC	Ongoing
BEVZ92	Phase 3 in patients with previously untreated mCRC	Ongoing
HD204	Phase 3 in patients with advanced nonsquamous NSCLC	Ongoing
BCD-021	Phase 3 in patients with NSCLC in combination with paclitaxel and carboplatin	Ongoing
Cetuximab		
STI-001	Phase 3 of biosimilar with irinotecan in 501 patients with colorectal cancer against irinotecan monotherapy	Significant improvement compared with chemotherapy alone in ORR, PFS, and OS according to press release; no published results yet

CHOP indicates cyclophosphamide, hydroxydaunomycin, vincristine, prednisolone; DLBCL, diffuse large B-cell lymphoma; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PCR, pathological complete response; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; TTP, time to progression.

and pharmacokinetic equivalence to rituximab.⁴² Meanwhile, the biosimilar BCD-020 demonstrated significant difference in overall relapse rate and safety compared with rituximab in 92 patients with follicular or marginal zone non-Hodgkin lymphoma.⁴³ A third rituximab biosimilar, RTX-M83, demonstrated comparable efficacy to rituximab in terms of tumor response, pharmacokinetic profile, pharmacodynamic activity, safety, and immunogenicity in patients with previously untreated CD20+ diffuse large B-cell lymphoma.⁴⁴

Bevacizumab. Bevacizumab biosimilar candidates include BCD-021, studied in patients with advanced nonsquamous non-small cell

lung cancer (NSCLC) in combination with paclitaxel plus carboplatin. There were no significant differences in efficacy or safety between the biosimilar and the reference product.⁴⁵ At least 5 other bevacizumab biosimilars are in late-stage clinical trials.⁴⁶

Cetuximab. One of the first biosimilars to be studied against a drug other than the reference biologic, STI-001, was investigated in EGFR-expressing metastatic colorectal cancer patients in combination with irinotecan versus irinotecan alone. The combination therapy showed significant improvement compared with chemotherapy alone with an overall response rate of 32.9% versus 12.8%, a

progression-free survival rate of 5.6 versus 3.2 months, and overall survival of 14.1 versus 13.4 months.⁴⁷ The manufacturer also reported significantly fewer adverse events than in studies of the reference product, with no hypersensitive reaction compared with more than 10% of patients in the cetuximab trials. The manufacturer attributed the difference to a different production method. However, the results have not yet been published, only announced in a 2016 press release. Several other cetuximab biosimilars are in early development.⁴⁸

Conclusions

As more patents begin to expire on oncologic biologics, the pace of biosimilar development in this therapeutic arena will pick up speed. At least 16 biosimilars are now in late-stage development and 2 are already approved (albeit not on the market as of March 2018). Their uptake in the oncology community, however, remains unclear. Challenges include physician and patient understanding of biosimilars versus biologics, particularly in terms of approval process; concerns over immunogenicity; pricing; interchangeability and substitution; cost; and supply chain issues. The option biosimilars offer, even at a 15% discount, will likely overcome these barriers as they move into the market and offer some promise for future treatments. ■

Additional Resources

FDA	fda.gov
European Medicines Agency	ema.europa.eu/ema
The Center for Biosimilars	centerforbiosimilars.com
Generics and Biosimilars Initiative	gabionline.net

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