REPORT

Recognizing and Addressing Challenges to the Adoption of Trastuzumab Biosimilars and HER2-Targeted Therapies

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ABSTRACT

Oncology biologics are one of the fastest-growing segments of pharmaceutical development, bringing more options to patients, including those with human epidermal growth factor receptor 2 (HER2)-positive breast cancer. The advent of multiple oncology biosimilars is affecting this patient population, as 5 trastuzumab biosimilars had been FDA approved as of the end of 2019; only 2, however, have been commercially marketed. Trastuzumab serves as the foundation for treatment for patients with HER2-positive breast cancer. HER2-targeted antibody–drug conjugates have been developed to enhance efficacy, improve safety, and/or create more convenient administration. Three biologic drug entities have been approved using trastuzumab, including 2 antibody–drug conjugates and a subcutaneous trastuzumab formulation that includes hyaluronidase. More products are being developed, so biosimilars and other HER2-targeted therapies may further disrupt the biologic market. Many challenging questions surround the adoption of oncology biosimilars, including regulatory pathways, efficacy, safety, cost-benefit, and comparability. The Biologics Price Competition and Innovation Act established an abbreviated regulatory approval pathway for biosimilars to create a catalyst for innovation and competition in the biologics market and to lower the costs of biologics. Challenges to adoption of therapeutic oncology biosimilars continue in the United States and include a lack of directed education to providers and patients, residual concerns regarding efficacy and safety, and practices including "pay-for-delay." The uptake of oncology biosimilars is also affected by multiple issues stemming mainly from cost of care, including drug cost, patient access, formulary inclusion, and treatment management algorithms. Managed care organizations and payers need to be familiar with the biosimilar approval process, the concerns of stakeholders (eg, providers and patients), and factors influencing HER2-directed therapies, including the use of biosimilars and antibody–drug conjugates in today's market.

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For author information and disclosures, see end of text.

Trastuzumab, a humanized monoclonal antibody (mAb) that is a human epidermal growth factor receptor 2 (HER2) receptor antagonist, is a biologic drug that serves as a foundation of the treatment of HER2-positive breast cancer in the neoadjuvant, adjuvant, and metastatic settings.[1] Additional trastuzumab indications include HER2-overexpressing metastatic gastric and gastroesophageal junction adenocarcinoma and cancers that are identified based on diagnostic testing.[2] For each year between 2014 and 2018, trastuzumab experienced annual worldwide sales of approximately $7 billion.[3,4] With the end of trastuzumab's US market exclusivity in 2019, biosimilars of the drug are expected to capture some of the market share. As of December 2019, 5 biosimilars of trastuzumab had been approved by the FDA, although only 2 are commercially available to date.[5] However, the manufacturer of trastuzumab has subsequently developed and marketed 2 additional HER2-directed therapies with some overlapping indications with the reference product: ado-trastuzumab emtansine (Kadcyla), a conjugate of the mAb and a microtubule inhibitor; and a combination product, trastuzumab/hyaluronidase-oysk (Herceptin Hylecyta).[6-8] Fam-trastuzumab deruxtecan-nxki (Enhertu), a HER2-directed mAb with a topoisomerase inhibitor conjugate, was also approved in late 2019, adding to the armamentarium.[9] As the availability of trastuzumab biosimilars and HER2-directed therapies increases, managed care professionals will face challenges that are primarily based on cost of care and can impact patient access, formulary decisions, and clinical care plans. To address those challenges, managed care professionals should understand the regulatory pathways for approval of biologics and biosimilars as well as understand the concept of antibody drug-conjugates.

FDA Biosimilars Regulatory Pathway

Introduction

The FDA regulates the approval of drugs through a variety of mechanisms. With the era of biologics and the passing of the Biologics Price Competition and Innovation Act (BPCIA), 3 pathways have been authorized for the approval of biologics: (1) the full 351(a) Biologics License Application (BLA) pathway, (2) an abbreviated

351(k) pathway for biosimilars, and (3) the 351(k)(4) pathway for interchangeable biosimilars.[10] This article will provide an overview of the nuances of these regulatory pathways, presenting them in comparison with the small-molecule drug approval pathway. The intent is to improve managed care professionals' understanding of biosimilars, including those used for oncology applications; HER2 antibody–drug conjugates will also be reviewed. With the current US approval of 5 biosimilars, a subcutaneous trastuzumab/hyaludronidase product, and 2 HER2 antibody–drug conjugates, this timely information will be useful in the context of treatment of HER2-positive breast cancer.

Small-molecule Generic Approval (Hatch-Waxman Amendments)

A perspective on small-molecule generic drugs is helpful because the law creating small-molecule generic drugs was a model for the law creating biosimilars. In addition, knowledge of the differences between small-molecule generics and biosimilars is necessary to properly educate patients and healthcare professionals. The term "generic drug" refers to "a medication created to be the same as an existing approved brand-name drug in dosage form, safety, strength, route of administration, quality, and performance characteristics."[11] The brand-name and generic drugs in question contain an active pharmaceutical ingredient (API) that can be synthesized chemically. By virtue of chemical synthesis, the API in a brand-name drug product and a corresponding generic drug product are identical. This key point is one of the major differentiating factors between generics and biosimilars.

The Drug Price Competition and Patent Term Restoration Act (colloquially referred to as the Hatch-Waxman Amendments) was passed in 1984 to establish a regulatory mechanism for the approval of small-molecule generic drugs as a means to rein in high drug prices.[12-14] To prompt competition in the prescription drug marketplace, the Hatch-Waxman Amendments "established bioequivalence as the basis for approving generic copies of drug products"[15] through the streamlined regulatory pathway called the abbreviated new drug application (ANDA), which was originally developed by the FDA in 1969.[14] Generic drug applications submitted through the ANDA process do not generally require original preclinical or clinical safety and efficacy data to gain FDA approval. The generic drug manufacturer must conduct clinical pharmacokinetic (PK) studies or, in certain instances, in vitro dissolution studies to demonstrate bioequivalence.[16] Thus, the generic drug applicant would have to establish that their product's API is identical to that of the brand-name product and that their product is bioequivalent.[13,15] Bioequivalence is determined if no significant differences in the rate and extent of absorption are demonstrated with the generic product compared with those of the brand-name product.

The goal of the Hatch-Waxman Amendments to lower drug prices has been successfully met. The addition of generic products to the market puts downward pressure on drug prices, with the greatest effects seen after 2 or 3 generic manufacturers introduce products.[17] Market research has shown that 6 months after a generic drug is launched, the generic products can capture 75% or more of the brand-name market share at a price discount of 40% or more.[18]

BPCIA of 2009

The BPCIA of 2009, which was a part of the Patient Protection and Affordable Care Act, codified the biosimilar class of drugs under the Public Health Services (PHS) Act.[10] The BPCIA also established an abbreviated regulatory approval pathway for biosimilars to spur innovation and competition in the biologics market as a means to lower the costs of biologics.[19-21] While the Hatch-Waxman Amendments were an inspiration for the BPCIA, there are several key differences between the laws.[14,19] One obvious distinction is that the BPCIA covers biologics, whereas the Hatch-Waxman Amendments addresses small-molecule drugs. The approach to FDA authority is substantially different between each legislation. With Hatch-Waxman, the FDA was required to create regulations that specify the types of data necessary for the ANDA process. However, as set out by the BPCIA, the FDA is not bound to a pre-established set of data for approvals via the streamlined 351(k) pathway, which has resulted in a stepwise, totality-of-evidence approach described by an FDA guidance document for industry in which the amount of clinical and preclinical data is determined on a case-by-case basis.[19,22] Under Hatch-Waxman, a single approval mechanism based on bioequivalence was created, whereas the BPCIA created 2 approval categories: biosimilar and interchangeable biosimilar. Market exclusivity of generic drugs and biosimilars differ as well. The first generic drug of a brand-name product benefits from 180 days of market exclusivity, whereas the first interchangeable biosimilar of a reference biologic would have interchangeable market exclusivity for 1 year under the BPCIA.[19,22,23] A summary of the major differences between the Hatch-Waxman Amendments and the BPCIA are listed in **Table 1**.[19]

To further discuss the differences among an original biologic and its biosimilars and antibody–drug conjugates, a few definitions are helpful. The reference biologic or reference product is the original biologic that was approved and licensed under section 351(a) of the BPCIA (ie, the full BLA).[10,20,21,24] A biologic is deemed a biosimilar if it was approved and licensed under section 351(k) of the BPCIA.[10] A biosimilar is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences in terms of safety, purity, and potency.[10,22] Additionally, the biosimilar must have the same route of administration, dosage form, and strength as the reference product. An interchangeable biosimilar is a product

within a subset of biosimilars, as the interchangeable biosimilar would be approved and licensed under subsection 351(k)(4) of the BPCIA.[10] The makers of an interchangeable biosimilar, in addition to satisfying the biosimilar requirements, must demonstrate that their product would produce the same clinical result as the reference product in any given patient. They must also demonstrate that switching between the interchangeable and reference product in a single patient would not increase the risk of safety issues or diminished efficacy compared with using the reference biologic product alone.[10,25] The FDA has concluded that a product approved as an interchangeable biosimilar may be substituted for the reference product without consulting the prescriber, similar to the current practice with small-molecule generics. To date, no applications have been made for an interchangeable biosimilar following the FDA's final ruling in May 2019. Other HER2-targeted therapies, including HER2 antibody–drug conjugates, are licensed under the full 351(a) BLA process.[26-28] The Food, Drug, and Cosmetic Act (FD&C Act) 505(b)(1) and 505(b)(2) pathways have been used for certain biologics, most prominently, insulin products. Notably, as of March 23, 2020, biologics approved under the FD&C Act will be deemed biologics under the PHS Act.[29]

FDA Approval Process

The BPCIA does not mandate, within the legislation, the specific parameters that the FDA must use to evaluate and approve biosimilars or interchangeable biosimilars,[19,22] so the FDA has developed a number of guidance documents for the industry.[30] The FDA's guidance on demonstrating biosimilarity describes its perspective on the stepwise and totality-of-evidence approach.[22] The stepwise approach identifies 3 categories of studies, which are depicted in **Figure 1**[31]: comparative quality studies, comparative nonclinical studies, and comparative pharmacology and clinical studies.[22,31]

Studies Comparing Biosimilar With Reference Product

The comparative quality studies focus on characterizing and comparing the physicochemical, structural, and functional properties of the proposed biosimilar in relation to the reference product. Many of the biologics and biosimilars—particularly those used in oncology, including trastuzumab and its biosimilars (**Table 2**[5])—are mAbs.[31] Therefore, the physicochemical and structural characterization studies of these large proteins would include analyses of the molecular weight; primary amino acid sequence; the secondary, tertiary, and/or quaternary structure; polarity and/or charge; and posttranslational modifications, such

TABLE 1. Comparison of the Hatch-Waxman Amendments and Biologics Price Competition and Innovation Act (BPCIA)[19]

	Hatch-Waxman Amendments	BPCIA
Drugs affected	Small-molecule drugs	Biosimilars
Year enacted	1984	2010
Evidentiary threshold	Bioequivalence	2 strata: biosimilars or interchangeable biosimilars
Binding notice and comment rulemaking required by the FDA?	Yes	No
State of FDA regulation	Binding notice and comment rulemaking in 1994	Guidance documents without binding regulation
Clinical trial data necessary for approval	FDA not permitted to require	Case-by-case basis at FDA's discretion
Central repository products and equivalents or biosimilars	Yes: FDA Orange Book	Yes: FDA Purple Book
Follow-on manufacturer required to submit dossier to originator?	No	Yes
Market exclusivity for first follow-on product	180 days	Up to 1 year for interchangeable products only

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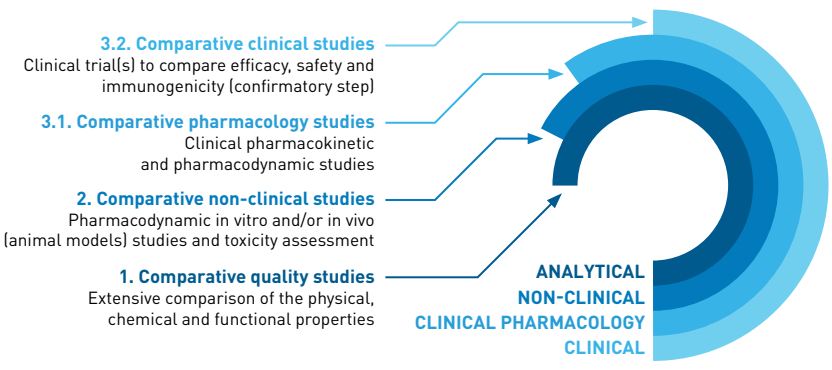
FIGURE 1. Stepwise Approach to Support Demonstration of Biosimilarity[31]



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as glycosylation. The functional properties would typically focus on assays that determine binding affinity for the specific target or receptor, which is HER2 for trastuzumab and its biosimilars.[31,32] Comparative nonclinical studies would focus on pharmacodynamic and toxicity tests conducted in vitro or in animal models. The clinical studies in humans are differentiated between comparative PK and pharmacodynamic (PD) studies and comparative efficacy, safety, and immunogenicity studies.[31,32] Whereas the 351(a) full BLA approval process for the reference biologic emphasizes clinical studies for each specific population and indication of use, the 351(k) pathway emphasizes the bioanalytical comparison between biosimilar and reference biologic, as illustrated in **Figure 2**.[32] For an interchangeable product, additional clinical PK and PD studies would be required; these would focus on the effect of switching back and forth—multiple times—between the proposed interchangeable biosimilar and reference product. The results would need to demonstrate that switching would pose no greater safety risks or diminished efficacy versus not switching from the reference product.[25,33]

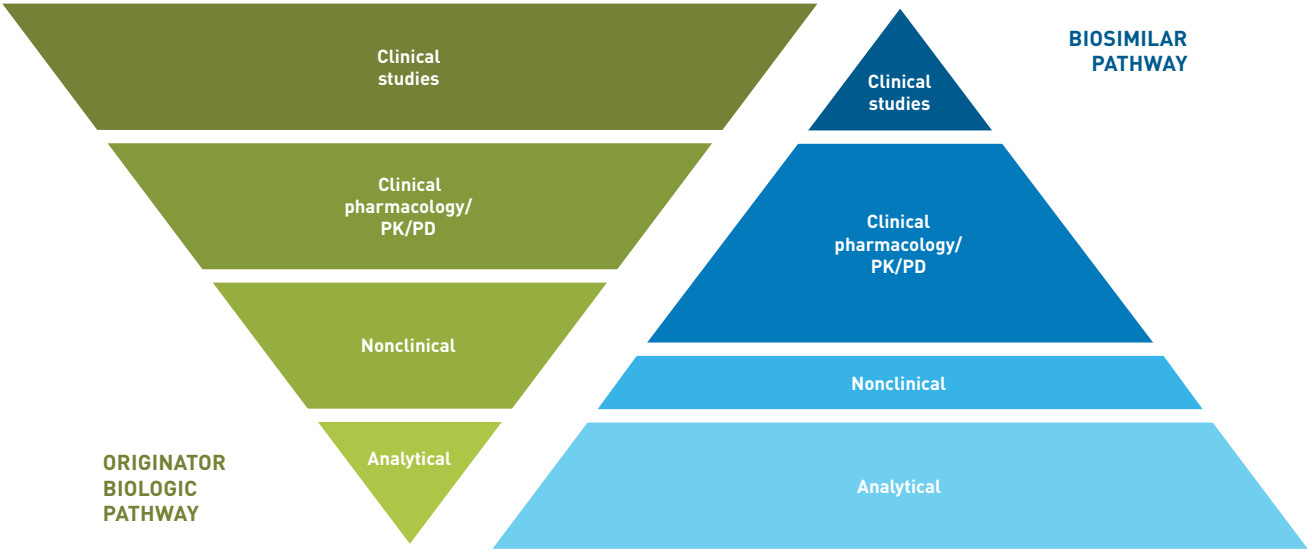
TABLE 2. FDA-Approved Oncology-Related Biosimilar Products as of December 2019[5]

Reference Product	Biosimilar	Approval Date
Bevacizumab	Bevacizumab-awwb*	September 2017
	Bevacizumab-bvzr	June 2019
Filgrastim	Filgrastim-sndz*	March 2015
	Filgrastim-aafi*	July 2018
Pegfilgrastim	Pegfilgrastim-jmdb*	June 2018
	Pegfilgrastim-cbqv*	November 2018
	Pegfilgrastim-bmez*	November 2019
Rituximab	Rituximab-abbs*	November 2018
	Rituximab-pvvr	July 2019
Trastuzumab	Trastuzumab-dkst*	December 2017
	Trastuzumab-pkrb	December 2018
	Trastuzumab-dttb	January 2019
	Trastuzumab-qyyp	March 2019
	Trastuzumab-anns*	June 2019

*Commercially marketed biosimilar.

By reviewing the totality of evidence for a biosimilar approval, the FDA may grant permission for the biosimilar to be used for 1 or more indications for which the reference product is indicated. This scientific and regulatory principle is called extrapolation, and it is an essential component of an abbreviated pathway. The biosimilar application must provide scientific justifications for extrapolation, including knowledge of the reference product's mechanism of action as well as its PK, PD, efficacy, safety, and immunogenicity in different key populations.[34] The FDA evaluates for any differences between the reference product and the proposed biosimilar and decides on a case-by-case basis to grant extrapolation to existing reference product indications.

FIGURE 2. Illustration of the Relative Emphasis of Analytical, Nonclinical, and Clinical Studies Between the 351(a) BLA and 351(k) Approval Pathways[32]



In addition to the preclinical and clinical studies necessary to support a BLA or 351(k) application, manufacturers of reference biologics and/or biosimilars must monitor safety issues associated with their products after marketing.[35] The FDA recently developed a draft guidance on best practices for postmarket safety surveillance.[36] The window for public comments closed as of January 2020, and the guidance may be finalized in 2020. A number of mechanisms are available for the pharmacovigilance and postmarketing surveillance of biologic products and biosimilars.[37] With the worldwide distribution of biologics, coordination with international agencies and standardization, where feasible, may facilitate rapid exchange of information.[38] Naming conventions for biologics and biosimilars, as discussed in the following sections, can contribute to or deter from accurate postmarketing surveillance and pharmacovigilance.

Types of Noninnovator Biologics

By establishing the 351(k) and 351(k)(4) approval pathways, the BPCIA effectively created 2 new classes of biologics—biosimilars and interchangeable biosimilars, respectively. The differences among these classes and among reference biologics have been described previously. The 351(k) pathway has been used successfully by noninnovator manufacturers, as 24 biosimilars have been approved by the FDA as of December 2019, with 12 biosimilars commercially marketed.[5] Whereas an application has not yet been submitted via the 351(k)(4) pathway, the recent finalization of the interchangeability guidance may spur activity in that area.[39]

The issue of interchangeability has been somewhat contentious, particularly for the wording in the BPCIA that defines an interchangeable product as one that meets "the standards described in section 351(k)(4)" and subsequently "may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product."[10] Providers have been concerned about the lack of communication required for interchangeability. As the responsibility of regulating interchangeability rests at the point of dispensing (ie, at the state level), 45 US states and Puerto Rico have passed legislation to regulate interchangeable biologics.[40] Although each law differs, the legislation of some states features provisions that require notifying the prescriber if anything but the originally prescribed product will be dispensed, or to allow the prescriber to specify a particular biologic drug. These provisions include, but are not limited to, allowing the prescriber to designate "dispense as written" or an analogous designation; specifying notification or communication from the pharmacist to the prescriber when a substitution is made; notifying the patient when a substitution will be made or is made and obtaining patient consent prior to substitution; providing legal immunity for pharmacists who make an interchange that is in compliance with applicable laws; and requiring the state to maintain a list of FDA-approved interchangeable products.[40] With interchange regulations varying by state, managed care professionals and pharmacists must be aware of current laws for their particular jurisdiction once an interchangeable biologic is approved.

Noninnovator as well as innovator manufacturers may also use the standard 351(a) full BLA pathway for approvals. This approach has been used to effectively create other HER2-targeted approaches. Strategies for modifying a reference biologic to create a different biologic include creating new strengths or formulations to facilitate alternative routes of administration; conjugating molecules to the mAb to increase half-life (eg, pegylation); altering the glycosylation of the mAb; and changing amino acid sequences, among others.[41] The FDA designates such agents as new, unique biologics.

Although an antibody–drug conjugate would require the more extensive clinical data required of a full 351(a) BLA application, there are advantages to pursuing this route. By using the 351(a) pathway, an antibody–drug conjugate, upon approval, has the market exclusivity reserved for a reference biologic, and the manufacturer also avoids the wait for patent expiration necessary for a biosimilar application.[41] Patient benefits may include enhanced efficacy, increased safety, decreased administration time, decreased frequency of administrations, and/or the availability of additional lines of therapy after progression on the originator biologic.

Biopharmaceutical manufacturers use a variety of approaches in development of other targeted strategies. Approaches include pegylation (eg, pegfilgrastim), which reduces the dosing frequency of biologics by decreasing clearance; optimizing glycosylation; antibody–drug conjugates (eg, ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki); and combination products with hyaluronidase to facilitate subcutaneous administration (eg, trastuzumab/hyaluronidase-osyk).[6,8,10,41-43] Several trastuzumab-antibody–drug conjugates are approved, and additional agents are in development that are designed to target HER2.[44]

Nomenclature

The naming of biosimilars has implications beyond differentiating products and manufacturers. The accuracy of postmarketing surveillance and pharmacovigilance is directly tied to the accurate identification of the product involved. With biologics and biosimilars, given the potential risk of immune reactions and the fact that APIs are not identical due to the size and complexity of the molecules, there is a particular need for nomenclature that identifies the biopharmaceutical manufacturer of a biologic or biosimilar product. The first biosimilar to be approved and marketed, filgrastim-sndz, was allowed a nonproprietary name that included the core name of the reference biologic and a 4-letter extension that identified its manufacturer.[45] Subsequently, the FDA drafted a guidance document on the nomenclature of biologics that, again, specified the use of the core name of the reference biologic, but the 4-letter extension would be a random sequence devoid of meaning. The

FDA draft guidance was finalized in January 2017; an additional draft guidance update was published in March 2019 that includes perspectives on naming interchangeable biologics and potential changes to naming vaccines.[46,47] The FDA guidance of 2017 is similar to that of the World Health Organization, which directs naming by using the nonproprietary name of the biologic followed by a "biologic qualifier" consisting of 4 random consonants and an optional 2-digit checksum.[48] A number of stakeholders opposed this naming convention, arguing that the random letter sequence would complicate postmarket surveillance and pharmacovigilance and possibly hinder the adoption of biosimilars.[49-51] Although the FDA naming convention guidance is nonbinding, there is a strong precedent to follow such guidance documents.

Challenges to the Adoption of Oncology Biosimilars in the United States

Differences Between European and US Models: Lessons to Learn From European Experience

Biosimilars have a longer history and a higher percentage of market share in the European Union compared with the United States. The first biosimilar in Europe was approved in 2006 by the European Medicines Agency (EMA),[52] 9 years before the first biosimilar was approved by the FDA.[34] As of May 2019, 53 biosimilars were approved by the EMA, 5 of which are biosimilars of trastuzumab.[53] A detailed market report, *The Impact of Biosimilar Competition in Europe*, by QuintilesIMS, highlighted 4 observations regarding biosimilar competition.[54] First, biosimilars increase price competition, an observation that is made even if just 1 biosimilar enters the market. Although competition drives down prices, there is a weak relationship between biosimilar market share and price. Second, the market penetration by a biosimilar can be limited by lowering the price of the reference biologic in certain instances. Third, the initial biosimilar to market tends to capture more of the market share compared with the second and subsequent biosimilars. Fourth, biosimilars can increase patient access via lower prices.[54] However, these lessons from Europe may not always be applicable to the United States due to the complexities of the US healthcare system and the heterogeneity of healthcare systems in Europe. The FDA published its Biosimilar Action Plan in 2018 to describe efforts designed to spur competition and innovation in the biologics and biosimilars markets.[55] Managed care professionals should stay abreast of the implementation of the plan as well as the impact on biosimilar market uptake and the effect on pricing of biologics and biosimilars.

Provider Concerns

For biosimilars to influence overall costs of therapy, including oncology treatments, they will need to secure a position in the marketplace. Physicians are a major stakeholder group with the most leverage for influencing the acceptance of biosimilars via their many roles within the healthcare system, including as providers and clinicians, valued key opinion leaders, biopharmaceutical scientists and executives, and members of formulary committees, among others.[56] For clinical oncologists, several areas of concern about biosimilars have emerged, and those areas have been articulated in a statement by the American Society of Clinical Oncology (ASCO).[57] The first area of concern encompasses naming, labeling, and other regulatory issues as they correlate to the ability to identify a product and evaluate the available product information to make informed clinical decisions. The second area of concern focuses on the safety and efficacy of biosimilars. Clinicians must have confidence that biosimilars are safe and effective to use in clinical practice, and postmarketing surveillance will likely play a major role in establishing that confidence. The third area of concern includes interchangeability, switching, and substitution. While the BPCIA permits substitution of interchangeable biologics, ASCO suggested that physicians and patients are made aware of any such substitution. The fourth area of concern is the value of biosimilars. The major types of payers in the United States (Medicare, Medicaid, and commercial) have different approaches to reimbursing biosimilars, and ASCO has argued for transparency of cost, reasonable compensation, and fair coverage. The fifth and final area of concern is prescriber and patient education. ASCO affirmed their commitment to provide education in the area of biosimilars.[57]

Given ASCO's status as a large and influential association of oncology clinicians, its statement carries much weight in addressing physician acceptance of biosimilars. Survey studies can provide data on physician knowledge and acceptance of biosimilars. Several such studies, some of which include oncology clinicians, tend to point to the need for more education on biosimilars.[58-60] In a recent paper by Cook et al, biosimilar knowledge and understanding was studied in a population of 77 oncology clinicians, including physicians, pharmacists, and advanced practice providers. A large percentage (74%) were unable to provide a satisfactory definition of "biosimilar," highlighting the need for education. According to this small sample of clinicians, the most important factors involved in the decision to prescribe biosimilars are safety, efficacy, and cost.[60] A systematic review by Leonard et al identified 4 key areas of provider concern: immunogenicity, clinical trial evidence, extrapolation, and interchangeability. Although the review was more heavily weighted toward European attitudes, given the availability of published studies, the identification of common areas of concern can be used to tailor educational efforts.[61]

Additional concerns from the pharmacist perspective should also be acknowledged and include inventory issues (eg, stocking multiple biosimilars to cover varying payer policies), potential errors in billing based on dispensing a particular biosimilar or reference biologic, and maintaining accurate electronic health records.[62] These

concerns could all impact health-system and practice financials in procurement costs and errors affecting reimbursement from payers.

Patient Concerns

The general population and patients in health advocacy groups need education about biosimilars. In a survey study of 3198 individuals in the United States and the European Union, the general population had minimal awareness of biosimilars.[63] In the European Union and the United States, 66% and 70% of the general patient population responders, respectively, had never heard of biosimilars. At the highest level of biosimilar awareness measures ("has at least a general impression"), the percentages were 6% for both the general population responders in the United States and European Union and 20% and 30%, respectively, for patients in advocacy groups in the United States and the European Union ($P < .05$).[63] A small study of oncology patients (79 responders) in Colorado was conducted. Of the survey responders, 70% or more were able to identify the correct definition of biosimilars; 80% or more correctly answered questions regarding the regulation, reporting of adverse effects, and cost issues of biosimilars.[64] Whereas much of the cited research is not specifically focused on oncology, the issue of general biosimilar knowledge and understanding is insightful for application to oncology. There is evidence of a clear need for educating patients about biosimilars, and pharmacists can be important communicators of that information.

The Nocebo Effect

As biosimilars become more frequently used, clinicians have been describing the nocebo effect, whereby a negative symptom or outcome on treatment is reported in the absence of a pharmacologic effect.[65] Kristensen et al identified 3 key triggers for the nocebo effect: (1) negative information about a drug, (2) lack of knowledge regarding biosimilars, and (3) lack of coherence in information from healthcare professionals.[65] Educating patients on the potential adverse effects associated with a drug may increase the potential of the nocebo effect, which has been observed with small-molecule drugs.[66] In their systematic review of double-blinded and open-label studies involving biosimilars, Odinet et al observed higher discontinuation rates for infliximab biosimilars in open-label studies. However, wide variability in the reviewed studies and trends for fewer injection-site reactions with etanercept biosimilars were among the reasons that the authors could not come to a definitive conclusion on the nocebo effect with biosimilars.[66]

Managed Care/Payer Concerns

The uptake of biosimilars, including trastuzumab biosimilars, will be affected by myriad and often competing interests and concerns. Biopharmaceutical companies that produce reference biologics may not readily acquiesce their market position, as evidenced in part by aggressive patent litigation that often delays the marketing of biosimilars.[28,67] At times, patent litigation ends in a settlement between the parties that may include delay in biosimilar launch. As of July 2019, 4 of the 5 trastuzumab biosimilar developers reached settlements with the manufacturer of the reference biologic.[68] Such settlements, which have been used for generics and biosimilars, have been described as "pay-for-delay" agreements that have drawn notice by the Federal Trade Commission.[69] From the payer and managed care perspectives, the disproportionate costs of biologics may seem unsustainable. Biologics accounted for 38% of prescription drug spending in the United States in 2015, despite only 1% to 2% of the population being treated with a specialty pharmaceutical.[70] The potential savings from biosimilars, estimated between $24 billion and $150 billion over the period of 2017 to 2026, are critical to managing the rising costs of biologics.[70] For just trastuzumab, the cost savings possible with increasing market share of biosimilars was estimated to be between $208.0 million and $623.9 million, at a 25% and 75% biosimilar market share, respectively.[71]

The cost of biologics and biosimilars is a key factor in determining which drugs are available to which patients—but there is no such thing as a single, simple cost. Rebate agreements, which can amount to 50% of list price, between manufacturers and pharmacy benefit managers can drive formulary decisions to be made to give preference to reference biologics and to limit formulary access to biosimilars.[72] Restrictive formulary decisions can create scenarios of de facto therapeutic interchanges whereby only a specific biosimilar is available on formulary for a given reference biologic. Thus, if a reference biologic is prescribed, only the particular biosimilar would be eligible for reimbursement.[62] Dolinar et al made this point using the example of different rapid-acting insulins, while cautioning that therapeutic exchange will likely be a challenge for biologics and biosimilars.[73]

Complexities of biosimilar reimbursement via Medicare and whether a biologic is covered under Part B or Part D can result in higher out-of-pocket costs for the patient.[67] One particular analysis calculated how reference product manufacturer discounts would result in increased out-of-pocket expenses (estimated increase of $1686 per year) for Medicare Part D beneficiaries receiving an infliximab biosimilar.[74] The Biosimilars Forum, an advocate for biosimilars, recently proposed a set of policy incentives to increase the use of biosimilars and decrease costs. The proposed legislative mandates and their estimated savings (for the 2020-2029 budget window) include support of patient out-of-pocket costs in Medicare Part B ($1.9 billion-$5.2 billion in federal spending and $2.2 billion-$3.3 billion in patient out-of-pocket costs), increased access to biosimilars via a shared savings model with providers (up to $3 billion in federal spending), and use of an enhanced average sales price reimbursement for biosimilars ($1.6 billion-$8.2 billion in federal spending).[75] Although such savings may be difficult to

achieve, alternative policy models are likely necessary to facilitate biosimilar uptake in the United States with corresponding savings in healthcare expenditures.

With the potential for cost savings, payer and provider practices are starting to set policy decisions around oncology biosimilars. As examples of payer decisions, UnitedHealthcare recently announced specific biosimilars as preferred products over the reference biologics and other biosimilars for bevacizumab and trastuzumab,[76] and Aetna's policy on short- and long-acting granulocyte colony-stimulating factors identifies preferred biosimilars for those drugs.[77] Practice sites are also making preferred biosimilar decisions. A physician-led community oncology network, OneOncology, announced in 2019 their preference for biosimilars of bevacizumab and trastuzumab from a single manufacturer.[78] Although these examples are helpful anecdotes that may not necessarily suggest a widespread increase in clinical adoption of oncology biosimilars, they serve as indicators of acceptance. However, the examples also illustrate the concerns regarding the complexities of multiple policies affecting biosimilar prescribing and dispensing. As a sign of pending legislative changes that may also affect biosimilar use, the 116th US Congress has acted on a total of 51 bills, and introduced 29 bills as of February 13, 2020, that refer to biosimilars in the title or text of the proposed legislation.[79] Managed care professionals and pharmacists should be aware of future changes to payer policies and federal and state laws regarding biosimilars.

Conclusions

Since 2015, the FDA has approved 24 biosimilars for 9 reference biologics, but only 12 biosimilars have been commercially marketed as of the end of 2019. Within those marketed, there are still challenges to widespread adoption that range from lack of understanding of the approval pathway, to concerns around safety, efficacy, and interchangeability, to patent litigations. In spite of these challenges, biosimilars offer a potential benefit by reducing treatment costs and increasing patient access to therapy. Of the 5 approved trastuzumab biosimilars, the utilization of the 2 that are currently marketed will test whether therapeutic oncology biosimilars can be viable and reduce the US yearly sales of the reference drug. It is important to understand how antibody–drug conjugates and subcutaneous trastuzumab/hyaludronidase may impact the use of reference trastuzumab and trastuzumab biosimilars. In comprehending the challenges and concerns surrounding biosimilars and other HER2-targeted approaches and their potential market impact, managed care professionals can begin to make progress in addressing the rising healthcare costs associated with biologics. ■

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