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Managed Care Considerations for Navigating Biosimilar and HER2-Directed Therapies for the Treatment of HER2-Positive Breast Cancer

HIGHLIGHTS

Supplement to *The American Journal of Managed Care®*

Managed Care Considerations for Navigating Biosimilar and HER2-Directed Therapies for the Treatment of HER2-Positive Breast Cancer

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Intended Audience

Pharmacists and managed care professionals

Activity Overview

This activity will inform pharmacists and managed care professionals about the challenges to the increasing availability of trastuzumab biosimilars and other human epidermal growth factor receptor 2 (HER2)-targeted therapies, including HER2 antibody–drug conjugates. The activity will review aspects of FDA drug approval processes by comparing the regulatory pathways of small-molecule generics and biosimilars. Challenges to the adoption of biosimilars, with an emphasis on trastuzumab, will be discussed. This supplement was developed with the goal of providing pharmacists and managed care pharmacists with an understanding of the landscape of current and emerging availability of trastuzumab biosimilars and other HER2-directed therapies to treat HER2-positive breast cancer, with a focus on considerations that would assist in developing managed care strategies to optimize patient outcomes.

Statement of Educational Need

Oncology biologics are one of the fastest-growing segments of pharmaceutical development, bringing more options to many patients, including those with breast cancer. These therapies are generally large, complex molecules that are more difficult to characterize than small-molecule drugs. A biosimilar is defined as a biologic that is highly similar, but not structurally identical, to an existing FDA-approved biologic agent. The complexity of biologic agents mandates that, under the FDA, biosimilars be subject to different rules and regulations than small-molecule generic products. Trastuzumab biosimilars serve as an important example of complexity in the biosimilar market and can provide alternative treatment options for patients with HER2-positive breast cancer. Many unresolved questions surround the use of oncology biosimilars, including efficacy, safety, cost-benefit, comparability, and regulations. In order to meet these challenges, pharmacists need to be well versed in the issues surrounding treatment advances in HER2-positive breast cancer, particularly in the role of trastuzumab and its biosimilars and HER2-targeted therapies. As new breast cancer biosimilar and antibody–drug conjugate products enter the market, managed care professionals, pharmacists, and payers must be well informed regarding therapeutic options and their role in the treatment of HER2-positive breast cancer. Continuing education will improve managed care professionals' and pharmacists' competency in comparing biosimilars and managing HER2-positive breast cancer.

Educational Objectives

Upon completion of this activity, participants will be able to:

- Compare the regulatory pathway for FDA approval of biosimilar products with that of small-molecule generic products.
- Identify challenges to evidence-based adoption of trastuzumab biosimilars and other HER2-targeted therapies.
- Compare trastuzumab biosimilars and HER2 antibody–drug conjugates for HER2-positive breast cancer and assess their role in breast cancer treatment.
- Incorporate trastuzumab biosimilars and HER2 antibody–drug conjugates into formulary discussions, clinical care plans and processes, and educational initiatives for healthcare providers and patients.

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OVERVIEW

Through this supplement to *The American Journal of Managed Care®*, pharmacists and managed care professionals will increase their knowledge and understanding of the challenges to the increasing availability of trastuzumab biosimilars and HER2 antibody–drug conjugates. Challenges to the adoption and implementation of these agents, with an emphasis on HER2-positive breast cancer and the use of trastuzumab, will be highlighted.

TABLE OF CONTENTS

A Supplement to *The American Journal of Managed Care®* PROJ ACE0158

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REPORT

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

Jeremy Whalen, PharmD, BCOP

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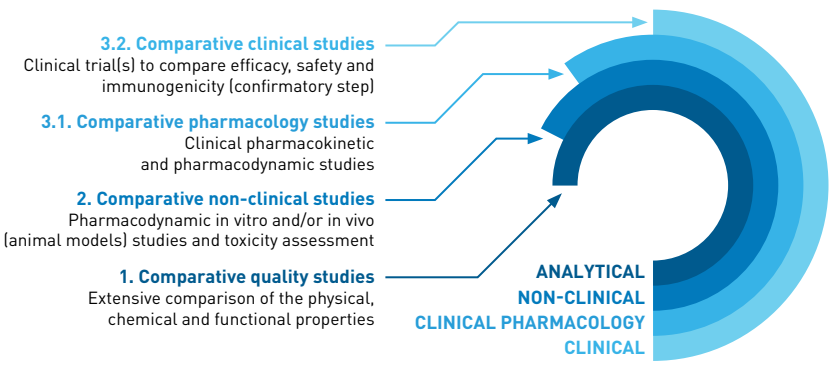
FIGURE 1. Stepwise Approach to Support Demonstration of Biosimilarity[31]



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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]

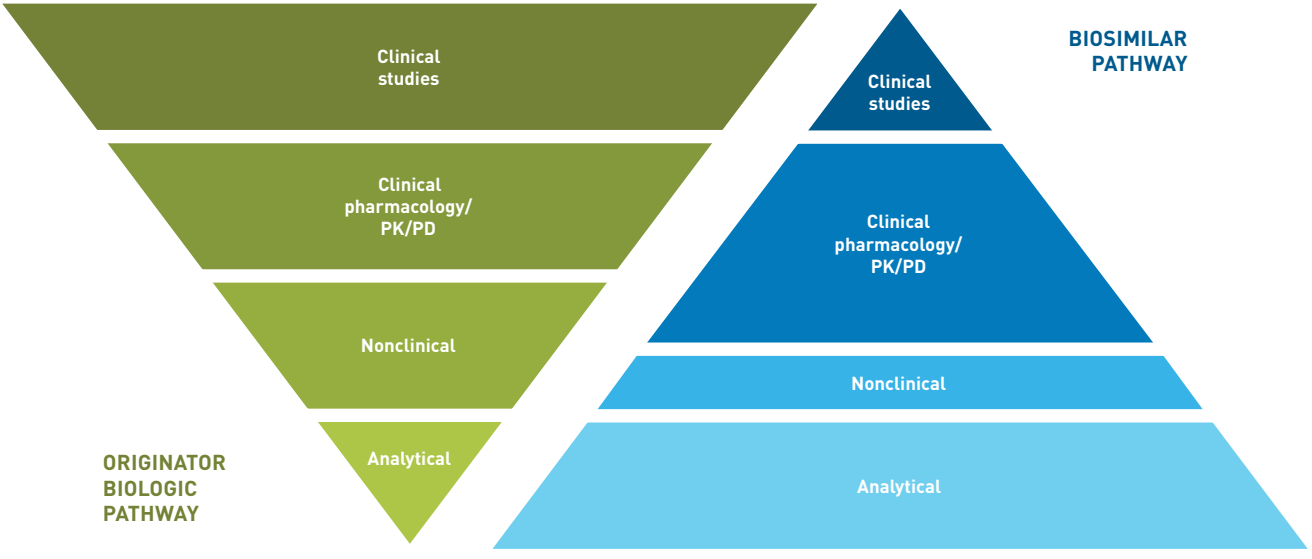
TABLE 2. FDA-Approved Oncology-Related Biosimilar Products as of December 2019[5]

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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REPORT

Integrating Trastuzumab Biosimilars and HER2-Directed Therapies into HER2-Positive Breast Cancer Management

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ABSTRACT

The approval of the humanized monoclonal antibody trastuzumab in 1998 changed the trajectory of treatment and subsequent outcomes for patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer and is now the standard of care in the neoadjuvant, adjuvant, and metastatic settings. However, as with most biologic drugs, trastuzumab comes with a relatively high price tag compared with traditional cytotoxic chemotherapy and contributes to healthcare budgets. Three engineered products related to trastuzumab—2 antibody-drug conjugates, ado-trastuzumab emtansine and fam-trastuzumab deruxtecan-nxki, as well as the subcutaneous trastuzumab/hyaluronidase—have since been approved and have expanded the treatment options for this patient population. The approval of 5 trastuzumab biosimilars as of the end of 2019 holds the promise of considerable cost savings, but challenges to integrating their use into patient care must be addressed. Barriers to their use, including physician uncertainty to switch patients from the reference drug to the therapeutic biosimilar and patients' lack of understanding about biosimilars, are common in the United States. It is also important that all stakeholders, including managed care professionals, pharmacists, and practice administrators, understand how to incorporate trastuzumab biosimilars into formulary discussions, clinical care plans and processes, and educational initiatives for healthcare providers and patients.

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For author information and disclosures, see end of text.

Introduction

An estimated 268,600 new cases of invasive breast cancer were diagnosed in women in 2019, making it the most common cancer in women in the United States. Although approximately 42,260 women died from the disease that year, the overall death rate from breast cancer has fallen by 40%, from 33.2 per 100,000 in 1989 to 20.0 per 100,000 in 2016.[1] This is due not only to earlier diagnosis through screening but also to the emergence of agents with new mechanisms of action and more targeted therapies that address the presence or absence of 3 key molecular markers in breast cancer: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2). These molecular markers are the basis for classifying breast cancer into 3 subtypes—HER2-positive, hormone receptor-positive (ER+ and/or PR+), or triple-negative—and for determining the appropriate initial treatment approach in early-stage disease.[2] Genomic and molecular testing is now standard practice in patients with advanced-stage breast cancer in order to determine the most appropriate targeted therapies based on hormone and HER2 status as well as *PIK3CA*, *BRCA1*, *BRCA2,* and *PD-L1* biomarker status.[3]

An estimated 15% to 20% of women with newly diagnosed breast cancer have tumors that overexpress HER2. These tumors tend to be more aggressive, more likely to invade lymph nodes, and more likely to recur and metastasize than other subtypes. They have also been historically associated with shorter patient survival compared with hormone receptor–positive breast cancer.[2,4] However, with the 1998 approval of trastuzumab, a humanized monoclonal antibody (mAb) that targets the extracellular domain of the HER2 protein, the trajectory of HER2-positive breast cancer shifted dramatically. Based on substantially improved outcomes in multiple clinical trials, including significant survival benefits across all stages of the disease, trastuzumab-based regimens are considered the gold standard of treatment for women with HER2-positive breast cancer.[2,3]

Trastuzumab

Cochrane Database of Systematic Reviews found that trastuzumab-based regimens in early breast cancer (EBC) improved overall survival (OS) by 33% (hazard ratio [HR], 0.66; 95% CI, 0.57-0.77; P <.00001)

and disease-free survival (DFS) by 40% (HR, 0.60; 95% CI, 0.50-0.71; $P < .00001$),[5] and in the metastatic setting improved OS by 18% (HR, 0.82; 95% CI, 0.71-0.94; $P = .004$) and progression-free survival by almost 40% (HR, 0.61; 95% CI, 0.54-0.70; $P < .00001$).[6]

Dosage and Administration

Trastuzumab has a variety of dosing regimens, with the dose, combination of agents, and duration depending on its use in the neoadjuvant, adjuvant, or metastatic setting. Trastuzumab is administered via intravenous (IV) infusion and requires a loading dose followed by a maintenance dose. The National Comprehensive Cancer Network (NCCN) lists 10 potential regimens in the preoperative and adjuvant settings.[3]

The NCCN guidelines list 4 potential trastuzumab-containing regimens for metastatic treatment in premenopausal women with trastuzumab in combination with an antiestrogen, either as monotherapy or in combination with lapatinib. For postmenopausal women, the preferred regimens are pertuzumab, trastuzumab, and docetaxel (category 1) or pertuzumab, trastuzumab, and paclitaxel. Several other regimens are also recommended.[3] The NCCN notes that an FDA-approved biosimilar is an appropriate substitute for trastuzumab in all settings.[3]

Safety

Overall, trastuzumab is well tolerated and does not require any supportive care medications before or after administration. The most common adverse effects (AEs) affecting at least 5% of women in the adjuvant setting are headache, diarrhea, nausea, and chills (most grade 2 in severity), whereas fever, chills, headache, infection, congestive heart failure, insomnia, cough, and rash were the most common AEs affecting at least 10% in the metastatic breast cancer (MBC) setting.[7,8]

Trastuzumab labeling carries a black box warning of the risk of cardiomyopathy. In the pivotal phase 3 clinical trial published by Slamon and colleagues, combining trastuzumab with anthracyclines caused cardiac dysfunction and heart failure in up to 27% of patients with metastatic disease compared with 7% in the anthracycline monotherapy group.[9] Since then, large observational studies have also identified higher rates of cardiotoxicity in women receiving trastuzumab compared with anthracycline alone.[10,11] This led to a change in clinical trial design to give the 2 drugs sequentially rather than concurrently, which demonstrated a much lower rate of cardiovascular effects.[12] Whether the cardiovascular changes are reversible when trastuzumab is discontinued remains a key question.[12]

Trastuzumab/hyaluronidase-oysk

Trastuzumab/hyaluronidase-oysk received FDA approval in February 2019. The product uses a patented drug delivery technology to facilitate subcutaneous (SC) administration, with recombinant human hyaluronidase (also called rHuPH20) acting as a temporary spreading factor. It degrades hyaluronan, a large glycosaminoglycan that otherwise limits SC administration of large volumes of fluid.[13] Although delivered SC, this product is not self-administered and must be administered by healthcare professionals in an outpatient setting.

Trastuzumab/hyaluronidase-oysk was compared with trastuzumab IV in the open-label, phase 3, noninferiority HannaH (Enhanced Treatment with Neoadjuvant Herceptin) trial. Eligible patients received 8 cycles of chemotherapy with either fixed-dose SC trastuzumab/hyaluronidase-oysk (600 mg) or IV trastuzumab (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) every 3 weeks in the neoadjuvant setting. Patients received an additional 10 cycles of SC trastuzumab/hyaluronidase-oysk or IV trastuzumab (according to their initial randomization) for 1 year following surgery.[14]

Rates of grade 3 or higher AEs were similar in the 2 groups, with neutropenia, leukopenia, and febrile neutropenia most common. However, 21% of patients in the SC group versus 12% of patients in the IV group had serious AEs, primarily infections and infestations (8.1% vs 4.4%).[15] With 6 years of follow-up in the 591 women in the intention-to-treat population, the event-free survival rate of 65% (HR, 0.98; 95% CI, 0.74-1.29) with an 84% OS (HR, 0.94; 95% CI, 0.61-1.45) were similar between the SC and IV study groups.

The faster administration time provides a much improved experience for patients as demonstrated in the PrefHER and MetaspHer studies. Results of the multicenter, crossover PrefHER trial, which randomized 240 women undergoing neoadjuvant or adjuvant treatment for HER-positive breast cancer to 4 cycles each of IV trastuzumab or SC trastuzumab/hyaluronidase-oysk, found that 91.5% of women preferred the SC formulation primarily because they spent less time in the clinic.[16] Similar results were seen in the MetaspHer study, which randomized 113 women to 3 cycles of trastuzumab/hyaluronidase-oysk SC or trastuzumab IV, followed by 3 cycles of the IV formulation.[17] Several studies have been conducted outside the United States attesting to the cost-savings potential of an SC delivery approach for healthcare systems; the savings are accrued from less preparation and delivery time as well as direct medical cost savings.[18-24] However, with the quickly evolving biosimilars market, the cost-savings potential of an SC delivery approach is not yet known in the United States.

It remains unknown if trastuzumab/hyaluronidase-oysk SC delivery will pose a threat to uptake of the biosimilars, all of which are administered by IV.[25] This version of trastuzumab does increase the potential for reducing the cost of trastuzumab IV therapy by adding more market competition. In evaluating costs, stakeholders must consider the complete episode of care; these include differences in drug administration costs and in revenue potential between the 2 different routes in practice settings.

The phase 3 PERSEPHONE trial was designed to investigate the hypothesis, demonstrated in other studies, that 6-month adjuvant trastuzumab treatment is noninferior to 12-month delivery.[26] The open-label, noninferiority trial randomized 4089 patients with HER2-positive EBC to either 6-month or 12-month trastuzumab delivered every 3 weeks IV or SC in combination with chemotherapy. Switching from the IV to the SC route was allowed at the prescriber's discretion. Eighty-two percent of the trastuzumab cycles were given IV and 18% were given SC. The 6-month cohorts met the primary end point of DFS noninferiority to 12 months of treatment, with increased adherence and fewer cardiac and other serious AEs in the 6-month group.[26] A cost analysis estimated an average savings of $12,800 for 6 months of trastuzumab versus 12 months, regardless of administration route, for a 100% cost-effective approach with no decrease in quality of life.[27] If such a change were adopted as a standard of practice with biosimilars, the cost savings could be even more significant.

Economic Issues Related to Trastuzumab

As with most biologics, the cost of trastuzumab started high and has continued to climb, even as other biologics with similar mechanisms of action entered the market.[28] One potential reason for this price increase is that there has not been competition in the marketplace prior to the advent of trastuzumab biosimilar, SC trastuzumab/hyaludronidase-oysk, and antibody–drug conjugate approvals. Trastuzumab has consistently ranked in the top 20 drugs for sales revenue in the United States, with sales of $2.87 billion in 2018.[29]

Although trastuzumab's high price does not limit access for patients with the need for lifesaving treatment in the United States due to coverage of the therapy by Medicare Part B as well as Medicaid plans, there are significant financial impacts to organizations—including practices and health systems—and to patients due to out-of-pocket costs. The cost-effectiveness of trastuzumab with or without concurrent or consecutive therapies in the neoadjuvant, adjuvant, and metastatic setting has been extensively studied, but results vary depending on the setting, breast cancer stage, and treatment regimen.[30-33] In a survey of 45 US oncologists, one-third cited high out-of-pocket costs for patients as a barrier to prescribing trastuzumab in the early and curative stages, and 10% reported at least 1 instance of delaying or canceling treatment because of reimbursement issues. Reimbursement issues also played a role in 60% of instances in which physicians did not prescribe the drug in the metastatic setting.[34] In the same survey, one-third of physicians reported that they would increase the use of HER2-positive antibody therapy if a lower-cost biosimilar version of trastuzumab were available.[34]

Ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki, and Other Antibody–Drug Conjugates

The impact of antibody–drug conjugates on the overall cost of care for patients with HER2-positive breast cancer is not yet known and complicates the landscape. These agents carry different indications than the reference trastuzumab product, and supportive care management also varies. **Table 1**[35,36] highlights indications and dosing of these agents.

Ado-trastuzumab emtansine is an antibody–drug conjugate. This antibody–drug conjugate links a microtubule inhibitor to a mAb. After the mAb binds with the tumor cell, the cytotoxic drug is delivered into the tumor cell where the "payload" is released. The rationale is to kill cancer cells and spare normal cells from toxicity, thereby potentially increasing efficacy and decreasing toxicity.[37]

Ado-trastuzumab emtansine was first approved in 2013 to treat HER2-positive MBC that was previously treated with trastuzumab and a taxane. A later study in patients with EBC led to its 2019 approval for adjuvant treatment of HER2-positive EBC in patients with residual invasive disease after neoadjuvant taxane- and trastuzumab-based treatment.[35] That indication was evaluated in the KATHERINE trial, a multicenter, open-label study in 1486 patients with HER2-positive EBC previously treated with neoadjuvant taxane- and trastuzumab-based therapy. Patients were randomized to adjuvant ado-trastuzumab emtansine or trastuzumab for 14 cycles. The interim analysis at 3 years estimated 88.3% of patients in the ado-trastuzumab emtansine group were free of invasive disease compared with 77.0% in the trastuzumab group. Invasive DFS was significantly higher in the ado-trastuzumab emtansine group than in the trastuzumab group (HR for invasive disease or death, 0.50; 95% CI, 0.39-0.64; P <.001). Distant recurrence as the first

TABLE 1. HER2 Antibody–Drug Conjugates Breast Cancer Indications and Dosing[35,36]

Generic Name (Brand Name)	Indication* and Dosing	Dosing
Ado-trastuzumab emtansine (Kadcyla)	1. Metastatic disease in patients who previously have received trastuzumab and a taxane, separately or in combination 2. Adjuvant treatment**	3.6 mg/kg IV every 3 weeks until disease progression or unacceptable toxicity (metastatic) or a total of 14 cycles (EBC)
Fam-trastuzumab deruxtecan-nxki (Enhertu)	Unresectable or metastatic cancer in patients who have received ≥2 anti-HER2–based regimens in the metastatic setting	5.4 mg/kg IV every 3 weeks until disease progression or unacceptable toxicity

EBC indicates early breast cancer; HER2, human epidermal growth factor receptor 2; IV, intravenous.
*All indications include HER2-positive breast cancer.
**Adjuvant treatment of patients with HER2-positive EBC who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

invasive-disease event occurred in 10.5% of patients in the ado-trastuzumab emtansine group and 15.9% of those in the trastuzumab group (HR, 0.60; 95% CI, 0.45-0.79). The benefits were sustained across all subgroups, including patients with hormone receptor-positive or -negative disease.[38] Patients in the ado-trastuzumab emtansine cohort were more likely to discontinue therapy due to AEs or to require a dose reduction than those in the trastuzumab group. They also experienced higher rates of serious AEs (12.7% vs 8.1%). The most common grade 3 or higher events in this group were decreased platelet counts and hypertension.[38]

Although ado-trastuzumab has been incorporated into national guidelines, an economic analysis of the agent as a second-line therapy compared with lapatinib plus capecitabine found it was not cost-effective from either a payer or societal perspective at a willingness-to-pay threshold of $150,000 per quality-adjusted life-year, although there was some suggestion that it might be cost-effective compared with capecitabine monotherapy.[3,39] The United Kingdom's National Institute for Health and Care Excellence also found that it was not cost-effective and thus does not recommend its use.[40]

Fam-trastuzumab deruxtecan-nxki was granted accelerated FDA approval in December 2019 based on data from the phase 2 DESTINY-Breast01 study.[41] This agent is an antibody–drug conjugate composed of a humanized anti-HER2 immunoglobulin G1 mAb, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor called DXd.[36] The DESTINY-Breast01 study was a multicenter, single-arm trial that enrolled 184 patients with previously treated metastatic HER2-positive breast cancer. The primary efficacy end point was objective response rate, which was reported to be 60.3% (95% CI, 53.4%-68.0%), with a 4.3% complete response rate and a 56% partial response rate. Median response duration was 14.8 months (95% CI, 13.8-16.9). The most common AEs (frequency >20%) were nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, neutropenia, diarrhea, leukopenia, cough, and thrombocytopenia.[42] The approval of fam-trastuzumab deruxtecan-nxki represents a therapeutic advancement and new option for patients with pretreated HER2-positive MBC.

Other HER2-directed antibody–drug conjugates are in clinical development, including [vic-] trastuzumab duocarmazine.[37] [Vic-] trastuzumab duocarmazine is composed of a recombinant humanized HER2 mAb covalently bound through a cleavable link to a duocarmycin prodrug, seco-duocarmycin-hydroxybenzamide-azaindole, known as seco-DUBA, which has cytotoxic activity. The safety and efficacy of [vic-] trastuzumab duocarmazine is being assessed in the open-label, randomized TULIP trial, comparing it with physician's choice treatment in women with HER2-positive, unresectable, locally advanced or MBC. In the phase 1 dose-escalation study, [vic-] trastuzumab duocarmazine was well tolerated, with ocular toxicity being the most commonly reported AE. Results from this trial are expected in 2021.[37]

The landscape of HER2-positive breast cancer continues to change with the addition of antibody–drug conjugates. These agents represent an advanced approach to cancer treatment that couples the specificity of mAbs to the cytotoxicity of classical chemotherapy agents, with potential for increased efficacy and manageable toxicity.

Trastuzumab Biosimilars

Five trastuzumab biosimilars have been approved in the United States for HER2-positive breast cancer as of late 2019: trastuzumab-anns, trastuzumab-qyyp, trastuzumab-dttb, trastuzumab-pkrb, and trastuzumab-dkst, although only 2 are available.[43] All major clinical trials for biosimilars demonstrated equivalence or noninferiority between the biosimilar and the reference drug with similar safety signals (**Table 2**).[44-53] However, the trials used different equivalence margins and were of relatively short duration in the adjuvant or MBC setting, which may be of some concern to clinicians.[54] These biosimilar trastuzumab studies used certain clinical end points, such as pathologic complete response (pCR) or overall response rate, which are ideal because they are sensitive enough to determine if a difference exists in terms of activity. In particular, pCR is important because the FDA has accepted it has a surrogate marker for survival; conversely, OS, a traditional end point, is not ideal because it accounts for all causes of death, not just those that are therapy related. Table 2[44-53] highlights key clinical efficacy and safety data.

As of 2019, trastuzumab-anns and trastuzumab-dkst are the only 2 biosimilars in this class that have been launched. Trastuzumab-anns entered the market just a few months after FDA approval without any patent settlement with trastuzumab manufacturer Genentech. Trastuzumab-dkst became available in late 2019.[55] The other 3 biosimilars have settled with Genentech and are expected to launch in 2020.[56]

The lag in launch of approved trastuzumab biosimilars has resulted in an estimated $140 million in savings lost in 2018.[57] However, once more biosimilars are on the market, the competition has the potential to increase the cost differential between the reference and biosimilar drug to more than the 15% discount at which trastuzumab-anns launched.[56] In Europe, the entrance of 3 trastuzumab biosimilars captured 38% of market share after just 10 months on the market, with sales of the reference product falling 16%.[56]

The true value of the trastuzumab biosimilars remains unclear. Just 1 study has been published on the potential cost-savings benefit of trastuzumab, and it was based on the Croatian healthcare system. It found that at a 15% lower cost than the reference drug, 14 additional patients could be treated; at a 35% discount, an additional 47 could be treated.[58] Nonetheless, it is important to consider analysts' expectations for cost savings from biosimilars overall. A 2017 RAND report estimated a potential $54 billion cost savings from biosimilars

TABLE 2. Trastuzumab Biosimilars: Indications, Trials, Efficacy, and Safety[44-53]

Biosimilar Generic Name (Brand Name)	Indication	Phase 3 Trial Design	Study End Points (Biosimilar vs Reference Product)	Most Common Serious AEs (Biosimilar vs Reference Product)
Trastuzumab-anns* (Kanjinti)	• Treatment of HER2-overexpressing breast cancer • Treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	• LILAC N = 725; EBC • Neoadjuvant therapy followed by adjuvant treatment up to 1 year	pCR: 48.0% vs 40.5%	• Neoadjuvant phase: 15% vs 14% (neutropenia most common) • Adjuvant phase: 9% vs 6% (neutropenia, infection most common)
Trastuzumab-dkst* (Ogivri)	• Treatment of HER2-overexpressing breast cancer • Treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	• HERITAGE n = 500; MBC • Biosimilar or reference drug plus taxane for 24 weeks then either alone until disease progression or loss of tolerability	• ORR: 69.6% vs 64.0% • TTP at 48 weeks: 41.3% vs 43.0% • PFS: 44.3% vs 44.7% • OS: 89.1% vs 85.1%	• Neutropenia (all grades): 57.5% vs 53.3% • Peripheral neuropathy (all grades): 23.1% vs 24.8% • Diarrhea (all grades): 20.6% vs 20.7%
Trastuzumab-pkrb (Herzuma)	• Treatment of HER2-overexpressing breast cancer	• N = 549; EBC • Neoadjuvant therapy with biosimilar or reference product plus docetaxel followed by adjuvant period up to 1 year; trial continuing	• Neoadjuvant: bpCR: 46.8% vs 50.4% • Adjuvant (24 mo): OS 97% vs 98%	6.6% vs 7.6%
Trastuzumab-qypp (Trazimera)	• Treatment of HER2-overexpressing breast cancer • Treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	• REFLECTIONS n = 707; MBC • First-line treatment with biosimilar or reference product plus paclitaxel	• ORR (week 33): 62.5% vs 66.5% • Median PFS: 12.16 mo vs 12.06 mo	34.4% vs 36.5% (neutropenia most common)
Trastuzumab-dttb (Ontruzant)	• Adjuvant and MBC • Metastatic gastric cancer	• N = 875 EBC or locally advanced • Adjuvant setting • Biosimilar or reference drug plus docetaxel and then FEC; in the adjuvant setting received drug only, some with radiotherapy/hormone therapy per local practice	• bpCR equivalent • CR: ER-negative and/or PR-negative (60.% vs 53%); ER+ and/or PR+ (46.9% vs 33.9%) • tpCR: 45.8% vs 35.8% • OS: 96.3% vs 91.2% • EFS at median follow-up (437 days for biosimilar and 438 days for reference product): 92.2% vs 91.6%; OS: 99.8% vs 98.9%	10.5% vs 10.7%

AE indicates adverse effect; bpCR, breast pathologic complete response; CR, complete response; EBC, early breast cancer; EFS, event-free survival; ER, estrogen receptor; FEC, fluorouracil/epirubicin/cyclophosphamide; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; ORR, overall response rate; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; PR, progesterone receptor; tpCR, total pathologic complete response; TTP, total time to progression.
*Indicates currently available.

in direct spending over a 10-year period. The report estimated that oncology mAbs would account for 13% of savings.[59]

Extrapolation

One area of significant concern among clinicians is the extrapolation of a biosimilar to all indications of the reference drug.[60] Currently, the FDA biosimilar approval process does not require separate clinical trials for each indication; however, manufacturers have to provide sufficient scientific evidence to support the determination of biosimilar status, such as knowledge of the structure, mechanism(s) of action, pharmacokinetics, and pharmacodynamics in each of its approved indications.[61] Clinically equivalent studies are required only if uncertainty remains. As shown in Table 2,[44-53] 4 biosimilars share the same indications for the reference drug, whereas trastuzumab-pkrb is indicated only for breast cancer. All indications are based on clinical trials for that disease rather than extrapolation.

Trastuzumab Biosimilar Uptake: Issues for Physicians, Payers, and Pharmacists

With trastuzumab biosimilars having been on the market for just a few months, it is difficult to predict how payers will incorporate them into formularies. For instance, infliximab remained on most formularies in 2017 despite the availability of a biosimilar at a 15% lower wholesale price. This suggests that payers must consider multiple factors other than cost in evaluating biosimilars for formulary decisions, which is usually of utmost importance when small-molecule generics enter the market. Considerations also include provider and patient relationships as well as concerns about efficacy and safety when the issue of switching to the biosimilar arises.[62]

However, the environment may be changing. As of October 1, 2019, UnitedHealthcare began requiring the use of trastuzumab-anns prior to the use of trastuzumab and other trastuzumab biosimilars.[63] Medicare Advantage plans are now able to use step therapy for Part B drugs, so it is possible they could institute similar requirements.[64]

Another factor that may slow adoption of the trastuzumab biosimilars is that federal and state laws allowing substitution (interchangeability) for generics do not apply to biosimilars. Only biosimilars with an interchangeable designation can be substituted for the reference product automatically. In most states, that substitution requires that the prescriber receive notification. In addition, rebates and discounts offered by the reference manufacturer may make the biosimilar discount less attractive.[62] However, payers could require therapeutic substitution as part of the formulary process.[65]

Physician Barriers to Trastuzumab Uptake

One of the greatest barriers to trastuzumab biosimilar uptake will be physician and patient reluctance to switch from the reference drug to a biosimilar, given the relatively modest cost reduction (most of which the payer accrues). Other barriers are concerns about efficacy and safety.[66]

Results from an online survey of 297 US physicians who prescribe biologics found that 84% did not favor a nonmedical switch to a biosimilar, despite the potential cost benefits. Physicians also expected that switching would negatively impact patient mental health, drug efficacy and safety, and physician office management.[67] Most physicians reported trying to avoid switching between biologics unless medically necessary. Those who did switch for nonmedical reasons (primarily payer requirements) did so to avoid higher costs; however, such switches can disrupt and delay treatment for patients who must deal with administrative issues through their insurance company.

Abundant data exist that appear to indicate no compromise of efficacy or safety when switching from a reference drug to a biosimilar. In a meta-analysis conducted by Cohen et al, 90 studies were evaluated in which more than 14,000 patients switched from a reference product to a biosimilar.[68] Cohen et al concluded that switching from reference product to biosimilar is not inherently dangerous, and patients and healthcare professionals should not be concerned about such switching. The authors did acknowledge that, as with all biologics, pharmacovigilance is important to monitor for rare safety events and for unexpected changes in efficacy or safety profiles. Of note, only 4 studies that were included in this meta-analysis were cancer-related trials, and those were primarily filgrastim studies.[68]

Numerous surveys report deficits in healthcare provider understanding of biosimilars. Results of one conducted among 376 US physicians and about 900 from European and Latin American countries found significant knowledge gaps regarding the effects of biologics versus biosimilars and whether they are structurally and therapeutically identical. The authors recommended educational initiatives "to dispel the misconception that biologics and biosimilars are structurally and therapeutically identical, and to promote a better understanding of their differences in order to improve patient care."[69]

In a survey of 1201 US physicians, including oncologists, 45% thought that biosimilars were safe and appropriate for both treatment-naïve and previously treated patients, 36% thought that biosimilars were not as safe as the reference biologic, and just 12% of physicians were comfortable with extrapolation of indications. The authors also noted the need for physician education.[60] The need for additional education to providers has been noted through multiple surveys. Regulatory bodies, including the FDA as well as oncology and pharmacy professional societies, offer courses, webinars, and presentations about specific aspects of biosimilar use from development of biosimilars to education that providers can use to educate their own patients.[70,71]

Results from a 2018 survey of 77 oncologists, pharmacists, and advanced practice providers found that 74% of respondents could not define a biosimilar or differentiate it from a generic drug. For these oncology clinicians, the most important attributes of a biosimilar were safety and efficacy, followed by cost differences. Clinicians disagreed about the importance of shared decision making with patients when it came to biosimilars.[72]

Meanwhile, a survey of more than 500 US hematologists and oncologists found that[73]:

- 58% (153 of 263 total respondents) said a biosimilar would have to be priced between 11% and 30% less than the reference drug for them to prescribe it.
- 66% (126 of 191 total respondents) said it was extremely important or very important to save costs by prescribing biosimilars versus reference products.
- 34% (20 of 59 total respondents) believed that the patient's financial responsibility would be lower for a biosimilar than an originator product all of the time, whereas 58% (34 of 59 total respondents) believed it would be lower some of the time.

Although respondents were initially "uncomfortable" about the regulatory process, the majority expressed a "reasonable" level of comfort after they received education about it. They also said they would like practice guidelines for when to prescribe a biosimilar versus a reference product, which are already available in current NCCN guidelines.[3,73]

Challenges for Pharmacists

As more trastuzumab biosimilars become available, pharmacists also may experience challenges; these might include operational issues, such as storing multiple biosimilars, updating electronic medical record order sets, documenting accurately, and billing correctly. Patient safety challenges also exist, as there is the potential to inadvertently prescribe, dispense, or administer an incorrect product. A recent survey of 300 managed care and specialty pharmacy professionals found that respondents had a generally favorable view of the safety and efficacy of biosimilars, even when switching from a reference product; however, just 54% supported extrapolation.[74]

When asked about strategies to improve provider updates of biosimilars, the majority (91%) selected educational programs for prescribers focused on switching strategies. The least favored strategy was requiring therapeutic drug monitoring for patients who switch in order to address concerns about immunogenicity. More than half (62%) cited concerns about safety and efficacy among patients as a difficult or somewhat difficult barrier to uptake, whereas half cited formulary management issues.[74]

In addition, the survey demonstrated significant variation in payer uptake of biosimilars, with about one-third of respondents reporting that biosimilar preferences were based primarily on contracting rebates. Nearly one-fourth revealed that their organizations have not established policies or preferences for biosimilars, pending additional safety and efficacy evidence.[74]

Pharmacists often lead discussions and preparation for formulary discussions on the inclusion of therapeutic oncology biosimilars and biologics. In addition to reimbursement and contractual agreements, multiple factors for biosimilar inclusion, such as whether the data support extrapolation of use for certain indications, safety profiles, and post-approval pharmacovigilance reports, must be considered.[75] For HER2 antibody–drug conjugates, it's important to consider not only efficacy data but also comparison of differences in safety and administration as well as how the biologic may replace use of existing formulary agents.

Patient Barriers

Patient attitudes are also key to biosimilar adoption, with surveys demonstrating mixed results. Results of a 2015 PricewaterhouseCoopers study found that 67% of consumers did not know what a biosimilar was, and just 17% were able to choose the correct definition from several choices.[76] Another survey administered to 3198 patients (including 76 with breast cancer), caregivers, advocates, and individuals in the general population in Europe and the United States found that just 6% of the general population had basic awareness of biosimilars; up to 70% of patients had never heard of them. Patients who were aware of biosimilars were more likely to believe that they were safe and more willing to switch to a biosimilar, indicating that increasing patient awareness could help increase uptake of these agents.[77] Patient acceptance may improve if collaborative relationships are established with patient advocacy groups. Patient advocacy groups such as CancerCare and Susan G. Komen have patient-centered online education and workshops on biosimilars. These online workshops often feature oncologists, healthcare providers, pharmacists, and oncology social workers on their panels.[78,79]

Another risk with patients is the nocebo effect, in which a negative effect of a medical treatment occurs because of the patient's expectation but is unrelated to the physiologic effects of the treatment. This can be particularly prevalent when switching medications and is expected to be a barrier to biosimilar switching.[80] One useful strategy for overcoming the nocebo effect is positive framing, which emphasizes benefits while maintaining transparency about the risks of switching to a biosimilar.[80] Training clinicians to use this kind of enhanced communication strategy has been shown to improve acceptance and persistence after switching to a biosimilar in rheumatology patients.[81] A provider who is knowledgeable about biosimilars and communicates well with patients can help overcome patient concerns as well. Providers can also use numerous tools, including patient-facing resources from the FDA, to direct patients to information that will help them understand the risks and benefits of biosimilars.[82]

Conclusions

With 5 trastuzumab biosimilars either currently on or entering the market, there is the potential for significant impact in the treatment of HER2-positive breast cancer. The approval of SC trastuzumab/hyaluronidase-oysk with modifications in route and administration as well as trastuzumab antibody–drug conjugates with differences in efficacy and safety are rapidly changing the landscape. The effects of these additions to the market share, and their subsequent cost implications, is not yet known. The complexity and cost of managing HER2-positive breast cancer continues to evolve. Biosimilars represent an opportunity to reduce cost of care without compromising quality of care. Pharmacists have an integral role in the appropriate use of these agents by leading discussions about formulary decisions and helping to balance clinical with financial considerations; these discussions would include such issues as interchangeability, extrapolation of indications, pharmacovigilance, immunogenicity, inventory management, and affordability. Pharmacists are critical in guiding healthcare providers and patients through transitions from reference biologic to biosimilar, whether starting with the biosimilar or switching from a branded biologic. Most importantly, they have an essential role in educating patients, other healthcare professionals, and payers on the clinical efficacy and safety of HER2-targeted therapy, as well as their potential to extend life-saving treatment to patients with HER2-positive breast cancer. ■

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POSTTEST

Managed Care Considerations for Navigating Biosimilar and HER2-Directed Therapies for the Treatment of HER2-Positive Breast Cancer

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Sample of Online Posttest

Choose the best answer for each of the following:

1. A manufacturer submits a new drug application to the FDA for a biologic drug through the section 351(k)(4) regulatory pathway. Upon approval, which term would describe that drug?

A. Follow-on biologic
B. Reference biologic
C. Biosimilar
D. Interchangeable biosimilar

2. When comparing small-molecule generic drugs with biosimilar drugs, which statement is most accurate?

A. The active pharmaceutical ingredient (API) in a generic drug formulation does not need to be chemically identical to that of the brand-name drug
B. A generic drug is required to complete one efficacy and safety clinical trial for FDA approval
C. The API in a biosimilar drug formulation does not need to be chemically identical to that of the reference biologic product.
D. The API in a biosimilar drug formulation must be chemically identical to that of the reference biologic product

3. In relation to biological drugs and biosimilars, the nocebo effect can be described as:

A. A positive subjective outcome observed when treating patients with a new biological drug
B. A negative objective outcome observed when treating patients with a new biological drug
C. A positive objective outcome observed when treating patients with a biosimilar
D. A negative subjective outcome observed when treating patients with a biosimilar

4. What is the most accurate definition of an interchangeable biosimilar?

A. Approval of a biosimilar for an indication other than that which was studied
B. Use of a different administration route of a biologic than what has been prescribed
C. Use of a reference biologic and biosimilar in the same patient
D. Substitution of a biosimilar for a prescribed reference product without intervention of the prescriber

5. A multitude of economic and legal barriers exist that have prevented widespread adoption of biosimilars in the United States. All of the following represent such barriers, EXCEPT:

A. Relatively low costs, compared with reference biologics, associated with bringing biosimilars to market
B. Formulary decisions of payers and pharmacy benefit managers
C. Complex regulatory requirements for interchangeable drugs
D. Reimbursement policies by payers for biosimilars

6. **AN is a 67-year-old woman with recurrent estrogen receptor–negative, progesterone receptor–negative, human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC). Her oncologist has recommended docetaxel, pertuzumab, and trastuzumab, but her medical benefit plan has a formulary-preferred agent of trastuzumab-dkst. Before agreeing to change any orders to this product, AN asks the oncologist if this agent is safe and efficacious. She also asks if it is any more cardiotoxic than trastuzumab. Which response is correct?**
   A. Overall response rates are lower, but the cardiotoxicity profile is better for the biosimilar.
   B. Overall response rates are equivocal, but the cardiotoxicity profile is better for trastuzumab.
   C. Overall response rates are equivocal, and cardiotoxicity profiles are similar.
   D. Overall response rates are better, and the cardiotoxicity profile is better for the biosimilar.

7. **HT is a 55-year-old woman being treated for HER2-positive MBC that has progressed after first- and second-line therapies. Which of the following is an antibody–drug conjugate that has been shown to have efficacy in pretreated patients and may be considered for HT's next treatment?**
   A. Pertuzumab
   B. Trastuzumab/hyaluronidase-oysk
   C. Trastuzumab-anns
   D. Fam-trastuzumab deruxtecan-nxki

8. **Educational initiatives to improve adoption of and minimize concerns related to biosimilars should include all of the following, EXCEPT:**
   A. Clinical and safety differences between reference and biosimilar products
   B. Evidence related to switching between reference and biosimilar products
   C. Resources targeted to patients and their caregivers
   D. Strategies for operational management of formulary changes

9. **A biosimilar may receive extrapolation of indications if its manufacturer:**
   A. Conducts clinical trials for all indications
   B. Receives permission from the reference drug manufacturer
   C. Demonstrates efficacy and safety in real-world, off-label use
   D. Provides sufficient scientific evidence to support such a determination

10. **What issue must be discussed when considering a HER2 antibody-drug conjugate for inclusion on a formulary?**
    A. Extrapolation of indications
    B. Switching studies
    C. Efficacy outcomes
    D. Formulary substitution

NOTES

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