NAMCP Medical Directors Spotlight Guide: Biosimilars in Oncology 2021

How Biosimilar Trends and Issues in Oncology Can Affect Strategy for Medical Directors of Purchasers, Plans, and Providers

JOURNAL of MANAGED CARE MEDICINE

This content is selected and controlled by the National Association of Managed Care Physicians and is funded by Coherus Biosciences and Sandoz, a Novartis division.

Coherus BIOSCIENCES

SANDOZ A Novartis Division

This content is selected and controlled by the National Association of Managed Care Physicians and is funded by Coherus Biosciences and Sandoz, a Novartis division.

JMCM

JOURNAL
OF MANAGED CARE
MEDICINE

4435 Waterfront Drive, Suite 101
Glen Allen, VA 23060
(804) 527-1905
fax (804) 747-5316

EDITOR-IN-CHIEF
J. Ronald Hunt, MD

PUBLISHER
Jeremy Williams

JOURNAL MANAGEMENT
Douglas Murphy
Communications Inc.
P.O. Box 71895
Richmond, VA 23255-1895
(804) 387-7580
fax (703) 997-5842

MANAGING EDITOR
Barry Barnum
barry.barnum@douglasmurphy.com

GRAPHIC DESIGN
Douglas Murphy Communications, Inc.

ISSN: 1094-1525. The *Journal of Managed Care Medicine* is published by NAMCP Medical Directors Institute. Corporate and Circulation offices: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060; Tel (804) 527-1905; Fax (804) 747-5316. Editorial and Production offices: P.O. Box 71895, Richmond, VA 23255-1895; Tel (804) 387-7580; Fax (703) 997-5842. Advertising offices: Sloane Reed, 4435 Waterfront Drive Ste 101, Glen Allen, VA 23060 Tel (804) 527-1905, Fax (804) 747-5316.

POSTMASTER: Send address changes to The Journal of Managed Care Medicine, 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.

BPA WORLDWIDE BUSINESS

Journal of Managed Care Medicine

The Official Journal of the NAMCP MEDICAL DIRECTORS INSTITUTE

A Peer-Reviewed Publication

NAMCP Medical Directors Spotlight Guide:
Biosimilars in Oncology 2021

TABLE OF CONTENTS

NAMCP Medical Directors Spotlight Guide: Biosimilars in Oncology 2021

How Biosimilar Trends and Issues in Oncology Can Affect Strategy for Medical Directors of Purchasers, Plans, and Providers

Dawn Holcombe, MBA, FACMPE, ACHE

Abstract

The mission of the National Association of Managed Care Physicians (NAMCP) Medical Directors Oncology Institute is to open the lines of communication between medical directors in managed care and practicing oncologists to help them jointly better navigate and understand what is happening in managed care and the daily management and practice of oncology. The NAMCP Medical Oncology Directors Institute brings resources and updates, strategic reviews, and key information to medical directors for insurers, employers, providers, and integrated delivery networks. Our unique Executive Councils focus on emerging technologies, oncology and value-based contracting for manufacturers and managed market leaders.

This guide presents an overview of the growing trends regarding biosimilars in oncology, as well as the challenges and issues for physicians and oncology management challenges from the health plan perspective. It discusses biosimilars in the context of the current landscape, utilization and evidence, impact on the costs of care, quality and payment reform and issues and strategies for plans and purchasers seeking policy and strategy solutions for oncology management. This guide is part of a series of activities and initiatives within the NAMCP Oncology Institute to support medical directors from purchasers, plans, and provider systems, and to eventually achieve greater collaboration that should lead to improved patient outcomes in oncology.

INTRODUCTION

BIOSIMILARS ARE A GROWING COST-effective alternative in the space of biologic medicine. Early development and adoption outside of the United States (U.S.) was followed by a far slower uptake within the U.S. For years, both payers and providers have taken time to consider the implications and utilization of biosimilars versus reference products. Recent expansion of value-based programs, both federal and private, as well as the operational and financial pressures brought upon the medical community by the Coronavirus pandemic, have led to a heightened focus on the potential for biosimilar products. Both treating providers and managed markets can influence the growing utilization of biosimilars through formularies, policy, clinical treatment protocols, and better understanding of the role that biosimilars play as an option for standards for value-based care. Despite national annual savings of over $240 million for Medicare, Medicaid, and the commercial market, projected potential annual savings of nearly $7.0 billion may be achievable. This paper explores the history, issues, concerns, and opportunities for managed care and provider strategies moving forward in the biosimilar space.

DEFINITION OF BIOSIMILARS

What is a Biologic?

To understand a biosimilar product, one must start by understanding a biologic product. Conventional medicines are commonly made from chemicals, with easily defined structures that can be replicated by following a chemical "recipe." In contrast, biologic medicines are derived from living organisms, like humans, animals, or microorganisms, such as yeast and bacteria. Biologic products are regulated by the U.S. Food and Drug Administration (FDA) and are used to diagnose, prevent, treat, and cure diseases and medical conditions.[1]

Because biologics generally come from living organisms, they vary by nature, and can have large and complex structures. Variations can result from the manufacturing process of these living organisms and lead to slight differences between manufactured

lots of the same biological product. Classified as "acceptable within-product variations, these differences are normal and expected. The FDA reviews and assesses a manufacturer's process and strategy to control "within-product variations, to ensure that the manufacturer produces biological products with consistent clinical performance.[2] Traditional, chemically derived products are generally identified as "small-molecule" drugs, while biologic products are referred to as "large-molecule" drugs, due to their larger size and more complex structure.[3]

Biological products can include a wide range of medical products, including vaccines, blood components, gene therapy, tissues, and proteins of a wide variety, including monoclonal antibodies and cell signaling proteins. Clinically, biological products may be used to treat patients with cancer, kidney diseases, diabetes, and autoimmune diseases.

Biologic products are valuable to patients as primary treatment options, but also consume a growing portion of the costs of care. *"While only 1 to 2 percent of the U.S. population is treated with a specialty drug each year – a category that includes biologics and other complex, often expensive drugs – biologics alone accounted for 38 percent of U.S. prescription drug spending in 2015 due to their high cost per dose, and for 70 percent of drug spending growth between 2010 and 2015."*[4]

The Drug Price Competition and Patent Term Restoration Act, commonly known as the Hatch-Waxman Act, of 1984 opened the door to the creation of generic drugs, but the legislation excluded creation of copy versions of biological drugs. Eventually that changed when federal legislation opened the door and created a regulatory approval pathway that would be shorter and less expensive, for copy-versions of biological drugs, than the costs of a full new biologic drug application.[5]

"Biologics have been approved for use in primary cancer treatment and supportive care since 1989. Primary treatment biologics include, but are not limited to, cetuximab, rituximab (chimeric mAbs targeting epidermal growth factor receptor and CD20, respectively), trastuzumab, and bevacizumab (humanized mAbs that inhibit human epidermal growth factor receptor 2 and vascular endothelial growth factor A, respectively). These biologics have been shown to improve clinical, health-related quality of life (HRQoL) and hematological outcomes. Biologics are not exclusive to primary treatment but have been developed for supportive oncologic treatment as well. Supportive oncologic treatment addresses the adverse events that are common with primary chemotherapy. Biologics in supportive oncology care include, but are not limited to, agents that help replenish hematologic components during and following chemotherapy. Epoetin alfa and darbepoetin are recombinant human erythropoietic proteins. Filgrastim and its analog, pegfilgrastim, are recombinant human granulocyte-colony stimulating factors (G-CSFs). The use of supportive care biologics with chemotherapy improves hematological response and has a positive effect on HRQoL." [6]

The Costs of Cancer Care Biologics in the United States

"In the U.S., total spending on cancer care has increased from $27 billion in 1990 to $124 billion in 2010, with spending projected to reach approximately $157 billion by 2020. Total costs of cancer care for the U.S. population are predicted to increase across all phases of care. Cost drivers include technological innovation, rising costs of hospitalizations, and a population-level increasing susceptibility to malignancy due to an aging demographic and increasing life span. Global spending on oncology and supportive care drugs reached $100 billion in 2014, with targeted therapy expenditures accounting for almost 50 percent of this amount. In the U.S., oncology drug expenditures, excluding supportive care agents, increased by 18.0 percent from 2014 to 2015. The fastest growing drug classes within oncology are mAbs and protein-kinase inhibitors, with mAbs accounting for 35 percent of U.S. oncology spending. U.S. sales figures in 2015 for three of the top 20 global products – bevacizumab, rituximab and trastuzumab – were $6.2 billion, $6.3 billion, and $5.6 billion, respectively. U.S. patients are shouldering an increasing share of these rising costs as health plans restructure their benefit designs, including a transition to high-deductible health plans with higher patient out-of-pocket costs from traditional fixed copay plans. The financial consequences of cancer treatment on patients and their families can be and has been a substantial burden. Given the high cost of cancer care, the need to balance health care provisions and associated budgets for the full range of conditions affecting population health, plus issues of patient access, value, and equity, all have become subjects of global discussion and debate." [7]

What is a Reference Product?

The FDA defines a reference product very specifically. *"A reference product is the single biological product, already approved by the FDA, against which a proposed biosimilar product is compared. A reference product is approved based on, among other things, a full complement of safety and effectiveness data. A proposed biosimilar product is compared to and evaluated against a reference product to ensure that the product is highly similar and has no clinically meaningful differences."* [8]

By 2020, the basic molecule patents for nine of the top 20 biologic drugs were slated to expire. Another eight oncology biologic drugs will see their patents expire between 2013 and 2024.[9] These expirations create opportunities for research and development of biosimilars to these reference products, and subsequently, to offer cost-effective alternatives.

What is a Biosimilar?

The FDA identifies a biosimilar as *"a biologic that is highly similar to and has no clinically meaningful differences in safety, purity or potency from another biologic that is already approved by the FDA (known as the original biologic or "reference" product). Biosimilars are made with the same types of natural resources as the original medication to which they were compared, are given the same way, have the same strength and dosage, and have the same potential side events. A biosimilar provides the same treatment benefits as the original biologic."* [10]

However, biologics cannot be identically copied, in the way that generic drugs can be produced as an identical copy of the chemical make-up of a small-molecule product. *"Biologic agents are manufactured using cell lines and processes exclusive to the manufacturer. There are multiple steps for cloning, selecting, and expanding the cell line, and then isolating and purifying the product. At multiple points during that process, variations that create clinically significant alterations can potentially occur. A different cell line, for example, might result in a difference in post-translational protein modification that can affect immunogenicity and alter a drug's pharmacokinetics and dynamics."* [11] In immune-mediated reactions (immunogenicity), the body recognizes that the biologic drug and biosimilar are foreign, and in turn, produces antibodies, which lead to decreased efficacy, and/or increased side events.[12] However, hypothetical immunogenicity concerns have not been observed to date with biosimilars.

The "highly similar to" criteria are met after extensive comparative analyses of the structure and function of both the reference product and the biosimilar, looking at purity, chemical identity, and bioactivity. As with batch-to-batch comparisons of all biologics, slight ("not clinically meaningful") differences (also considered "acceptable within-product" variations) are expected for both the reference product and the biosimilar. These are carefully controlled and monitored. Additional differences in clinically inactive components (such as a stabilizer or buffer) are also acceptable between the reference product and the biosimilar.

Biosimilar product manufacturers must also confirm in a clinical setting that the high similarity be demonstrated analytically. *"This is usually demonstrated through exposure (human pharmacokinetic) and response (pharmacodynamic) studies, assessments of clinical immunogenicity, and if needed, further clinical studies."* [13]

An FDA statement on Biosimilars emphasizes their role in evaluation. *"Before approving a biosimilar, FDA experts must conclude it is highly similar to the original biologic and that it has no clinically meaningful differences from the original biologic. This means you can expect the same safety and effectiveness from the biosimilar over the course of treatment as you would from the reference product. This thorough evaluation helps to ensure that all biosimilar products are as safe and effective as their reference products and meet the FDA's high standards for approval."* [14]

"In addition, the FDA tightly regulates the manufacturing of biosimilars. The same quality manufacturing standards that apply to the original biologic also apply to the biosimilar. It must be manufactured in accordance with ***Current Good Manufacturing Practice*** *requirements, which cover methods, facilities, and controls for the manufacturing, processing, packaging, or holding of a drug product. This helps to prevent manufacturing mistakes or unacceptable impurities and to ensure product quality."* [15]

THE PATHWAY TO BIOSIMILARS

Utilization and acceptance of biosimilars gained traction in other parts of the world long before the U.S. In 2003, the European Medicines Agency (EMA) was the first to develop and publish guidelines for biosimilars and the first biosimilar was launched in Europe in 2006. Canada published their guideline document *(Information and Submission Requirements for Biosimilar Biologic Drugs)* in 2010, and a subsequent update in 2016.

In the U.S, the Patient Protection and Affordable Care Act (PPAC Act) was signed into law in March 2010, that included the Biologics Price Competition and Innovation Act (BPCI Act) – an abbreviated approval pathway to licensure for biological agents that are demonstrated to be "highly similar" (biosimilar) or "interchangeable" with an FDA-approved biological product.[16] The goal of this pathway was to provide more treatment options, increase access to lifesaving medications, and potentially lower health care costs through increased competition.

Each of the EMA, Canada and the U.S. (FDA), regulations require that the efficacy of the biosimilar agent be comparable to those of the original agent. There are minor differences in how each regulatory agency defines a biosimilar but they agree firstly, that a biosimilar is not a generic, secondly, biosimilarity is established by extensive comparisons to an already approved "reference" product and biosimilar, and lastly, that analytical comparisons are the foundation of establishing biosimilarity.[17]

"To balance the BPCI Act abbreviated pathway for development and approval of biosimilar and interchangeable products with incentives to develop innovative new products, the BPCI Act also provides exclusivity to manufacturers of certain biological products. The FDA may not approve an application for a biosimilar or interchangeable product until 12 years after the date on which the reference product was first licensed." [18] Exhibit 1 shows some of the characteristics of most of these regulations.[19]

Exhibit 1: Characteristics of Global Regulatory Agencies for Biosimilars

Characteristic	European Medicines Agency	U.S. Food and Drug Administration	Health Canada
Analytical Data	• Concentration–activity levels, pharmacokinetics, pharmacodynamics data.	• Package Insert must be derived from that of the reference product. • Analytic studies demonstrating that the product is highly similar in structure and function (the more comprehensive the characterization, the more useful it will be in determining any requirement for further studies).	• Receptor binding studies should be conducted, when appropriate.
Clinical Data	• Pharmacokinetics, pharmacodynamics and immunogenicity assessment; pharmacodynamics study might be sensitive enough on its own. • Population sensitive to demonstrate equivalence. • Must also demonstrate safety and efficacy to a previously authorized reference biologic drug. • For an anticancer monoclonal antibody, disease-free survival, progression-free survival and overall survival are preferred.	• Pharmacokinetics, pharmacodynamics and immunogenicity assessment are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions. • Population sensitive to demonstrate equivalence. • Endpoint sensitive to detect clinically meaningful difference ("totality of the evidence" approach).	• Pharmacokinetics, pharma-codynamics, clinical efficacy and safety assessment. • Population in whom product is indicated unless otherwise justified. • Endpoint sensitive to detect clinically meaningful differences.
Substitution or Interchange-ability	• Substitution policies are within the remit of the E.U. member states.	• Possible, additional studies and different data is required. • Substitution initiated by a pharmacist requires an interchangeability designation.	• Substitution if initiated by physician is permissible. • Substitution initiated by a pharmacist requires an interchangeability designation within the remit of provinces.
Extrapolation of Indications	• Possible, based on the overall evidence of comparability provided from the comparability exercise and with adequate justification; if different mechanisms of action are relevant (or uncertainty exists) applicants should supply relevant data.	• Possible, based on scientific justification including mechanism of action pharmacokinetics and biodistribution in various patient populations, immunogenicity in various populations and differences in toxicities expected.	• Possible; should be justified based on mechanism of action pathophysiologic mechanism, safety profile in the respective conditions or populations (or both), and clinical experience with reference drug.
Post-Marketing Surveillance or Pharma-covigilance	• Same requirements as reference product. • Applicant should present risk-management plan in accordance with E.U. legislation and pharma-covigilance guidelines.	• Same requirements as reference product. • Should take into account any safety or effectiveness concerns; should have mechanism to differentiate between events associated with the product and those with reference product (four-letter identification suffix known as "biologic modifier").	• Same requirements as reference product. • Adverse drug reaction reports and periodic safety update reports required.
Labelling	• Summary of product characteristics must be derived from that of the reference product.	• Labels require "biosimilarity or interchangeability statement" describing the biosimilar or interchangeable product's relationship to its reference product.	• Product monograph must be derived from that of the reference product. • There should be no claims for bioequivalence or clinical equivalence.

Sources:

Prepared jointly by the European Medicines Agency and the European Commission, "Biosimilars in the EU: Information Guide for Healthcare Professionals, 2019, last accessed on Jan. 27, 2021 at https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf

N.A. Nixon, MD, M.B. Hannourf, PhD., S. Verma, MD, "The evolution of biosimilars in oncology, with a focus on trastuzumab", Perspectives in Oncology, Current Oncology Volume 25, Supplement 1, June 2018, last accessed on Dec. 3, 2020 at https://www.current-oncology.com/index.php/oncology/article/view/3942/2762

Government of Canada, "Biosimilar biologic drugs in Canada: Fact Sheet", Last modified: Aug. 27, 2019, last accessed Jan. 27, 2021 at https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.html#a16

Government of Canada, "Archived: Product Monograph Template - schedule D - Biosimilar Biologic Drug", Archived: Oct. 30, 2020, last accessed Jan. 27, 2021 at https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/product-monograph/product-monograph-template-schedule-biosimilar-biologic-drug.html

Government of Canada, "Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs", Last modified: April 20, 2017, last accessed Jan 27, 2021 at https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/information-submission-requirements-biosimilar-biologic-drugs-1.html#a235

U.S. Food & Drug Administration, "Biosimilars", last modified Feb. 3, 2020, last accessed Jan. 27, 2021 at https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars

What are Interchangeable Products, and are Biosimilars Interchangeable with the Reference Product?

The BPCI Act defined an interchangeable product as a biosimilar that meets additional requirements outlined in the Act. These additional requirements set forth in the law include an evaluation of the risk in terms of safety and reduced efficacy of switching back and forth between an interchangeable product and a reference product for products administered to a patient more than one time. An interchangeable biologic is a biosimilar for which additional clinical data is provided. It is not a quality designation.

While physicians are always able to substitute a biosimilar in place of a reference product, pharmacists seeking to make this change, would need to first gain approval from the prescribing physician. However, once a biosimilar product has earned FDA-approval as an interchangeable product with its reference product, it may be substituted at a pharmacy for the reference product without the involvement of the prescribing physician, much as generic drugs are routinely substituted for brand name drugs. **As of December 2020, there were no FDA-approved interchangeable biosimilar medications.** Biosimilars may, as of that point in time, be provided to patients only by direct prescription from the treating physician.[20] Additionally, the FDA goes on to state that *"biosimilars and interchangeable products can be used in patients who have previously been treated with the reference product (treatment-experienced), as well as in patients who have not previously received the reference product (treatment-naïve)."* [21]

Is a Biosimilar the Same as a Generic Drug?

In some ways, biosimilars and generic drugs are alike, in that they both are versions of brand name drugs and could offer more affordable treatment options to patients and treating providers. Biosimilars and generic drugs are each approved by the FDA through abbreviated pathways that avoid duplicating the costly clinical trials incurred by the manufacturer of the reference product when it was first developed and brought to market. In other substantial ways, biosimilars vary significantly from generic drugs. Generic drugs are chemical compounds that utilize the same active ingredients of the brand name drug. The generic drug manufacturer must demonstrate that the generic drug is bioequivalent to the brand name drug.

Biosimilars are derived from living organisms, not chemicals. A biosimilar manufacturer must demonstrate that their product is highly similar to the reference product, within "acceptable within-product" variations, except for minor differences in clinically inactive components. Biosimilar manufacturers must also demonstrate that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety and effectiveness.

Given the inherent complexity and variability of biologics, biosimilars are explicitly NOT generic drugs and should NOT be treated as such by patients, providers, pharmacies, and external benefits managers, in terms of utilization, reimbursement, or coverage policy.

FDA Determination of Biosimilarity — "Totality of Evidence"

For the FDA to grant biosimilarity, it looks at the "Totality of Evidence" of data that may encompass highly similar structural and functional characteristics, an assessment of toxicity in animal models, and clinical studies that confirm no clinically meaningful differences. Providers and payers with questions regarding the evidence for a biosimilar product can review the full determination on the FDA website.[22]

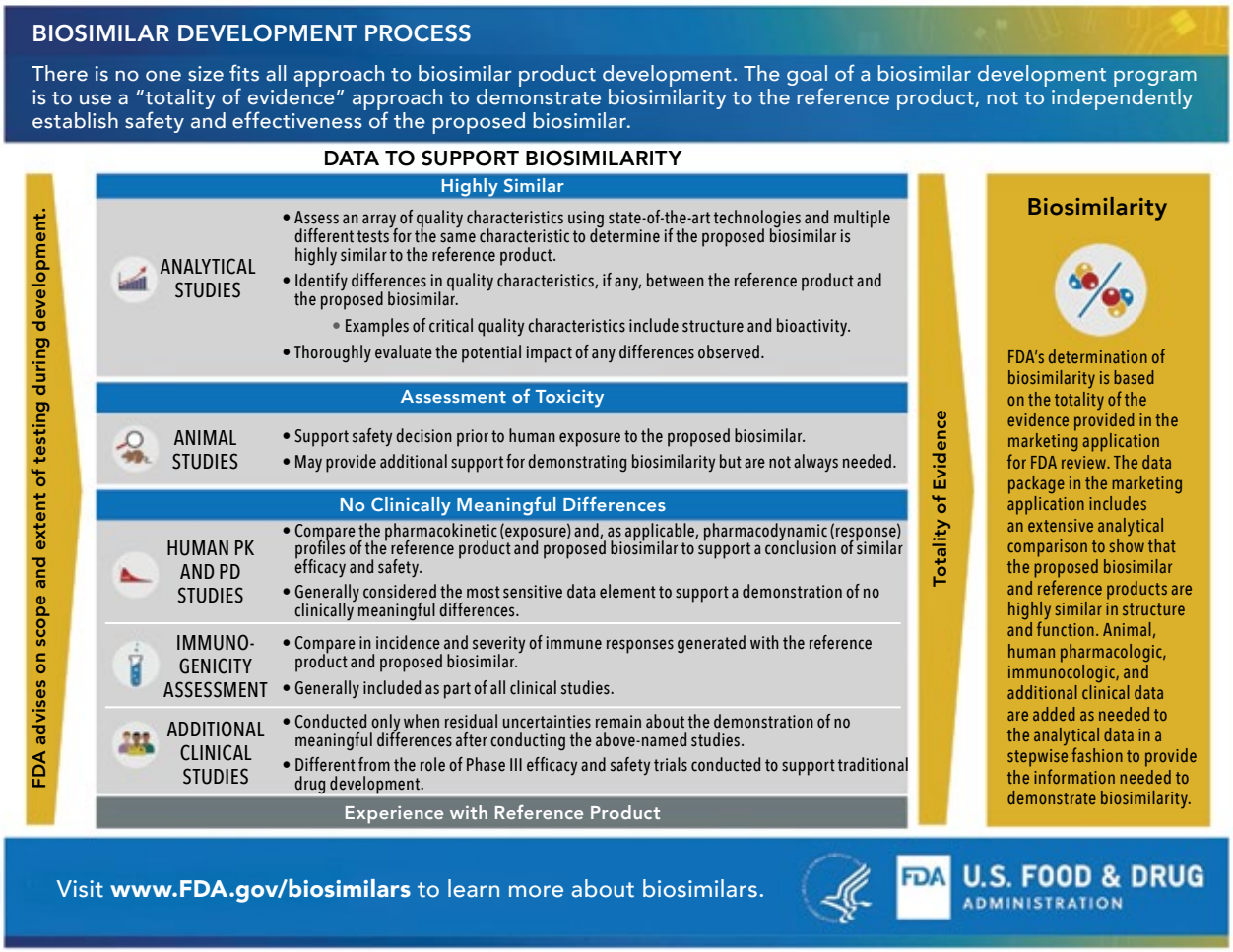
Exhibit 2 illustrates the FDA "Totality of Evidence" approach to demonstrate biosimilarity to the reference product. This approach does not independently establish safety and effectiveness of the proposed biosimilar since the goal is to measure against the reference product. Clinical studies are conducted to confirm the high similarity observed in the analytical studies. Given their design, the biosimilar clinical studies cannot by themselves establish that there are no clinically meaningful differences.

How Extrapolation is Applied for Biosimilars Approval

Extrapolation *"supports the use of an FDA-approved biosimilar product in indications that the reference product is approved for, for which the biosimilar product was not evaluated clinically. The justification for extrapolation is expected to address whether the same mechanism of action applies in each indication as well as the pharmacokinetic, biodistribution, and immunogenicity profiles in different populations. It is also expected to identify potential toxicities for each indication or patient population. However, in the U.S., a biosimilar may not be approved for any indication of the reference product protected by regulatory exclusivity, such as orphan drug or pediatric exclusivity. Although the extrapolation of data collected for a biosimilar reduces the need for duplicative clinical studies, it must be justifiably supported by scientific data, and thus regulatory agencies may differ in their approval decisions."* [23]

"Extrapolation is based on firstly, all available data and

Exhibit 2: U.S. Food and Drug Administration Biosimilar Development Process



Source:

U.S. Food & Drug Administration, https://www.fda.gov/media/113355/download

information in the biosimilar application, secondly, on the FDA's previous finding of safety and efficacy for other approved indications for the reference product, and lastly, on knowledge and consideration of various scientific factors for each indication. Extrapolation is not an assumption that the data from one directly studied indication or population alone is sufficient to support approval in a different non-studied indication or population. The biosimilar manufacturer must provide scientific justification to support extrapolation." [24]

Dr. Lee S Schwartzberg, MD, FACP, chief medical director of West Cancer Center explained biosimilar use in clinical practice as a balance, where the biosimilar agents can be successful for providers and patients but require thought and discrimination in utilization choices. The concept of extrapolation is key in the application of biosimilars.

"The regulatory definition [of extrapolation] from the FDA is that you do one clinical trial in a sensitive population, so you can pick up any difference whatsoever between the originator and the biosimilar. And if you get a result that shows equivalence, then you can extrapolate that into other settings in the same disease. But also, you can extrapolate that into any other approved indication for a particular drug," he said.

An example is trastuzumab, which is approved in gastric cancer and gastroesophageal junction cancers that are HER2-positive.

"The label for the trastuzumab biosimilars allows it to be used in those settings, even though it, to my knowledge, has not been tested extensively in gastric cancer. Most of the studies have been in HER2-positive

metastatic or early-stage breast cancer, because that's the overwhelming group that has this HER2 alteration."

This extrapolation concept is important also within breast cancer. Dr. Schwartzberg said. "If you're using a biosimilar that was tested in the neoadjuvant and adjuvant setting, it can also be used in the metastatic setting. So, if we have a patient with metastatic HER2-positive breast cancer for whom trastuzumab is indicated, which is virtually all of them, I feel comfortable also extrapolating and using it in that setting as well." [25]

FDA BIOSIMILARS ACTION PLAN

In 2018, the FDA published its Biosimilars Action Plan (BAP), expressing its commitment to take action to create a more competitive biosimilars market. Some of the key actions included are:

1. *"Developing and implementing new FDA review tools, such as standardized review templates that are tailored to enhance the public information about the FDA's evaluation of these products.*

2. *Creating information resources and development tools for sponsors of biosimilar applications. This includes such tools as in silico models and simulations to correlate pharmacokinetic and pharmacodynamic responses with clinical performance. These tools can make biosimilar drug development more efficient.*

3. *Enhancing the Purple Book to include more information about approved biological products, including information relating to reference product exclusivity determinations.*

4. *Actively exploring the potential for entering new data sharing agreements with foreign regulators to facilitate the increased use of non-U.S.-licensed comparator products in certain studies to support a biosimilar application.*

5. *Establishing a new Office of Therapeutic Biologics and Biosimilars (OTBB) to improve coordination and support of activities under the Biosimilars User Fee Act (BsUFA) program, accelerate responses to stakeholders, and support efficient operations and policy development.*

6. *Building on the FDA's Biosimilar Education and Outreach Campaign, continue providing critical education to health care professionals, including releasing a series of videos that explain key concepts about biosimilar and interchangeable products.*

7. *Publishing final or revised draft guidance on biosimilar product labeling to assist sponsors in determining what data and information should be included in the labeling.*

8. *Providing additional clarity for product developers on demonstrating interchangeability, including by publishing final or revised draft guidance.*

9. *Providing additional clarity and flexibility for product developers on analytical approaches to evaluating product structure and function to support a demonstration of biosimilarity, including publishing revised draft guidance on the use of data analysis methods, and statistical approaches.*

10. *Providing additional support for product developers regarding product quality and manufacturing process, including identifying physical product quality attributes that are most critical to evaluate, and by exploring ways to reduce the number of lots of the reference product required for testing.*

11. *Engaging in a public dialogue through a Part 15 hearing and opening a docket to request additional information from the public on what additional policy steps the FDA should consider as we seek to enhance our biosimilar program."* [26]

Key Elements of the FDA Biosimilars Action Plan

The BAP is focused on four key areas:

1. *"Improving the efficiency of the biosimilar and interchangeable product development and approval process.*

2. *Maximizing scientific and regulatory clarity for the biosimilar product development community.*

3. *Developing effective communications to improve understanding of biosimilars among patients, clinicians, and payors.*

4. *Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition."* [27]

FDA-APPROVED BIOSIMILARS

Applications under the new FDA biosimilar pathway began to be submitted in 2014. The first biosimilar product, filgrastim-sndz, (based upon the reference biologic filgrastim – a drug used to treat low white blood cell counts due to chemotherapy and other causes) was approved by the FDA for use in the U.S. in March 2015. This product was produced by Sandoz, based upon the reference product licensed by Amgen. Three other biosimilar products followed in 2016, five in 2017, seven in 2018, ten in 2019, and three in 2020, for a total of 29 as of December 17, 2020.[28]

The 29 FDA-approved biosimilar products are tied to just nine reference products, a reflection of maturation of the reference products and potential growth in competition fueled by interest from biosimilar manufacturers. Of those 29, only 16 have been brought to market as of December 20, 2020. Exhibit 3 illustrates the reference products linked to biosimilars.

Exhibit 3: U. S. Food & Drug Administration Approved Biosimilars as of Dec. 17, 2020

Reference Product	Biosimilar Product	Biosimilar Manufacturer	On Market as of 12/17/2020	FDA Approval Date
Avastin® (bevacizumab)	Mvasi™ (bevacizumab-awwb)	Amgen, Inc.	X	9/14/2017
	Zirabev® (bevacizumab-bvzr)	Pfizer, Inc.	X	6/27/2019
Enbrel® (etanercept)	Erelzi® (etanercept-szzs)	Sandoz, Inc.		8/30/2016
	Eticovo™ (etanercept-ykro)	Samsung Bioepis Co., Ltd.		4/25/2019
Epogen®/Procrit® (epoetin alfa)	Retacrit® (epoetin alfa-epbx)	Hospira, Inc.	X	5/15/2018
Herceptin® (trastuzumab)	Ogivri® (trastuzumab-dkst)	Mylan GmbH	X	12/1/2017
	Herzuma® (trastuzumab-pkrb)	Celltrion, Inc.	X	12/14/2018
	Ontruzant® (trastuzumab-dttb)	Samsung Bioepis Co., Ltd.		1/18/2019
	Trazimera™ (trastuzumab-qyyp)	Pfizer, Inc.	X	3/11/2019
	Kanjinti™ (trastuzumab-anns)	Amgen, Inc.	X	6/13/2019
Humira® (adalimumab)	Amjevita™ (adalimumab-atto)	Amgen, Inc.	Planned 2023	9/23/2016
	Cyltezo™ (adalimumab-adbm)	Boehringer Ingelheim Pharmaceuticals, Inc.	Planned 2023	8/25/2017
	Hyrimoz® (adalimumab-adaz)	Sandoz, Inc.	Planned 2023	10/30/2018
	Hadlima™ (adalimumab-bwwd)	Samsung Bioepis Co., Ltd.	Planned 2023	7/23/2019
	Abrilada™ (adalimumab-afzb)	Pfizer, Inc.	Planned 2023	11/15/2019
	Hulio (adalimumab-fkjp)	Mylan Pharmaceuticals, Inc.	Planned 2023	7/6/2020
Neulasta® (pegfilgrastim)	Fulphila® (pegfilgrastim-jmdb)	Mylan N.V.	X	6/4/2018
	Udenyca® (pegfilgrastim-cbqv)	Coherus BioSciences, Inc.	X	11/2/2018
	Ziextenzo® (pegfilgrastim-bmez)	Sandoz, Inc.	X	11/4/2019
	Nyvepria™ (pegfilgrastim-apgf)	Pfizer, Inc.	Planned 2020	6/10/2020
Neupogen® (filgrastim)	Zarxio™ (filgrastim-sndz)	Sandoz, Inc.	X	3/6/2015
	Nivestym® (filgrastim-aafi)	Pfizer, Inc.	X	7/20/2018
Remicade® (Infliximab)	Inflectra® (Infliximab-dyyb)	Celltrion, Inc.	X	4/5/2016
	Renflexis® (Infliximab-abda)	Samsung Bioepis Co., Ltd.	X	4/21/2016
	Ixifi™ (Infliximab-qbtx)	Pfizer, Inc.	Not planning to launch	12/13/2017
	Avsola® (Infliximab-axxq)	Amgen, Inc.		12/6/2019
Rituxan® (rituximab)	Truxima® (rituximab-abbs)	Celltrion, Inc.	X	11/282018
	Ruxience® (rituximab-pvvr)	Pfizer, Inc.	X	7/23/2019
	Riabni™ (rituximab-arrx)	Amgen, Inc.	Planned in 2021	12/17/2020**

Exhibit 3 Sources:

"How many biosimilars have been approved in the United States" Medically Reviewed by Judith Stewart, Bpharm, Drugs.com website, Last Updated on July 8, 2020, last assessed on Dec. 15, 2020 at https://www.drugs.com/medicalanswers/many-biosimilars-approved-united-states-3463281/

Zachary Brennen, "U.S. Biosimilar Launches About to Turn a Corner". Regulatory FocusTM web page on Regulatory Affairs Professionals Society website, Posted Mar. 16, 2020, last accessed Dec.16, 2020 at https://www.raps.org/news-and-articles/2019/12/us-biosimilar-launches-about-to-turn-a-corner

** "FDA Approves Amgen's RIABINTM (rituximab-arrx), A Biosimilar to Rituxan® (rituximab)", Amgen Press Release Dec. 17, 2020, last accessed on Dec. 19, 2020 at https://www.amgen.com/newsroom/press-releases/2020/12/fda-approves-amgens-riabni-rituximabarrx-a-biosimilar-to-rituxan-rituximab

MEDICARE AND PRIVATE PAYERS APPROACH TO BIOSIMILARS

Medicare Biosimilar Policy

Once the FDA had finalized a licensure process for biosimilars, Medicare followed by creating a distinct coverage policy on biosimilars. Medicare added a biosimilar policy in the 2016 Physician Fee Schedule Final Rule, in 42 CFR 414.904) (j), to set the payment amount for a biosimilar drug product based on the average sales price of all National Drug Codes (NDCs) assigned to the biosimilar products included within the same billing and Healthcare Common Procedure Coding System (HCPCS) payment code. Thus, Medicare was grouping biosimilar products that relied on a common reference product biologics license application into the same payment calculation, so that the products shared a common payment limit and billing code. Physicians were then reimbursed the same amount for all biosimilars of a common reference product. An add-on modifier for that common billing code was created to distinguish between biosimilars made by different manufacturers.

After significant feedback on the challenges of grouping several products together, and the issues caused by the blended codes related to pricing and tracking pharmacovigilance, Medicare adjusted the coding process for biosimilars just in time for several multiple products for a single reference product to hit the market. **The 2018 Medicare Physician Fee Schedule Final Rule rescinded the blending methodology and assigned individual "Q" HCPCS codes to each biosimilar product and changed reimbursement to the Average Selling Price (ASP) of the biosimilar plus 6 percent of its reference product. Since each biosimilar product now has its own assigned "Q" code, there is no longer a requirement to use a modifier to describe the product manufacturer.**[29]

Part of the feedback that led to these Medicare policy changes was that unique HCPCS codes for each individual biosimilar would increase the potential for innovation and ensure a robust, competitive biosimilar market. The pharmacovigilance concerns addressed potential confusion among providers who might have been willing to prescribe biosimilars, but accidentally continued prescribing the reference drugs under the old 2016 Medicare coding requirements. Separate, unique billing codes will reduce provider and payer confusion about whether a biosimilar is being utilized for a given patient. *"CMS' decision to assign separate HCPCS codes and payment rates to biosimilars will set the stage for a more vibrant and competitive biosimilars marketplace," said Amanda Forys of Xcenda, a part of AmerisourceBergen. "The new system could also increase awareness and adoption of biosimilars, as more manufacturers would contribute to provider and patient education initiatives to drive long-term uptake of these products. Patients will ultimately benefit as physicians could be more likely to use physician-administered biosimilars in their practices, leading to system-wide cost-savings and an increase of treatment options available to patients."* [30]

Does Federal Sequestration Affect Biosimilar Products?

Sequestration refers to an automatic reduction of certain federal spending, generally by a uniform percentage. Providers receive the 6 percent markup over the ASP to reflect their additional costs for storage, handling, and other administrative costs for drug products. The 6 percent has been reduced by a 2 percent sequestration adjustment for Medicare Fee-For-Service (FFS) and drug payments to Medicare Parts A and B participating providers, under the Budget Control Act from Fiscal Years 2013 through 2030.[31] That 2 percent sequestration payment adjustment was suspended temporarily for all Medicare FFS claims for claims with dates of service from May 1 through December 31, 2020 per Section 3709 of the Coronavirus Aid, Relief, and Economic Security (CARES) Act of 2020.[32] Since biosimilar products are paid as drugs under Medicare Parts A and B, their reimbursements are affected by the application of sequestration policies.

Private Payer Policies Lagged Medicare

There was at least a one-year lag in private payer acceptance of biosimilars behind Medicare, at least for cancer treatments. Pharmacy Benefits Managers (PBMs), as an intermediary for drug management for many private insurers and employers, reacted more quickly than many private insurers.

In 2016, PBMs declared coverage policies for biosimilars for non-oncology diseases, including diabetes and obesity. One year following the Medicare coverage policies, large national PBMs, including Express Scripts (the nation's largest PBM) CVS Health (the second largest U.S. PBM) announced that starting in 2017, the reference product of an insulin treatment was taken off their formularies and replaced with follow-on (but not "biosimilar") insulin drugs approved under the 505(b)(2) New Drug Application pathway (follow-on insulin drug approvals were transitioned in March 2020 to the 351(a) Biologics License Application pathway).[33] This was done under the argument that they felt it was appropriate to exclude a medication

because there was at least one clinically equivalent (or superior) product on the market that was more affordable for their clients, as noted in mid-2016 by David Whitrap, senior director for Corporate Communications at Express Scripts.[34] In 2018, Express Scripts dropped the filgrastim reference product completely off its preferred formulary while CVS Caremark restricted coverage of the reference filgrastim product in July 2017.[35]

United Health Care announced that its 2017 formulary would replace reference products for diabetes (insulin glargine) and cancer (filgrastim) treatments with other follow-on insulin biologics and filgrastim biosimilar products following similar exclusions announced by major pharmacy benefit managers, Express Scripts and CVS Health. Providers were not required to substitute the formulary alternative for the reference product but would have to go through extra steps to order the reference product if that were what they wished to prescribe.[36]

CIGNA prepared a Biosimilars Update in December 2018, noting that pricing of the eight biosimilars then on the market was not significantly discounted compared to the reference drug, and that providers still had limited experience with specific biosimilar products. The CIGNA biosimilar strategy was described as *"based on coverage of the lowest net cost option (LNC) between the biosimilar(s) and the reference product, in addition to evaluating clinical appropriateness. This strategy meant that the LNC could be either t he biosimilar or the reference product, as illustrated in Exhibit 4."* [37]

Most insurer policies became initially inclusive of biosimilar products, rather than choosing a tack

Exhibit 4: CIGNA Biosimilar Coverage Policies – January 2021

Reference Product	Biosimilar Name(s)	Coverage
Epogen®, Procrit®	Retacrit®	All are preferred brands and subject to medical necessity review.
Neulasta®	Ziextenzo®, Fulphila®, Udenyca®	Ziextenzo®, Fulphila® and Udenyca® are preferred brands and subject to medical necessity review. Neulasta® is a non-preferred brand and subject to medical necessity review.
Neupogen®, Granix®	Zarxio™, Nivestym®	Zarxio™ and Nivestym® are preferred brands and are subject to medical necessity review. Neupogen® and Granix® are non-preferred brands and are subject to medical necessity review.
Remicade®	Inflectra®, Renflexis®	All are preferred brands and subject to medical necessity review.
Avastin®	Mvasi™, Zirabev®	Mvasi™ and Zirabev® are preferred brands and subject to medical necessity review. Avastin® is a non-preferred brand and subject to medical necessity review.
Herceptin®	Kanjinti™, Ogivri®, Trazimera™, Herzuma®, Ontruzant®	Kanjinti™, Ogivri® and Trazimera™ are preferred brands and subject to medical necessity review. Herceptin7, Herzuma7 and Ontruzant7 are non-preferred brands and subject to medical necessity review.
Rituxan®	Ruxience®, Truxima®	Ruxience® and Truxima® are preferred brands and subject to medical necessity review. Rituxan is a non-preferred brand and subject to medical necessity review.

Exhibit 4 Sources:

"The U.S. Biosimilars market and Cigna affordability strategies", Cigna Pharmacy Management® CLINICAL UPDATE, published December 2018, last accessed Dec. 20, 2020 at https://www.cignaproducer.com/pdf/Cigna_Biosimilars_Update_Flyer.pdf, with Cigna Drug and Biologic Coverage Policy Updates last accessed Jan. 27, 2021 as follows:

"Erythropoiesis Stimulating Agents (ESA)"—https://static.cigna.com/assets/chcp/pdf/coveragePolicies/pharmacy/ph_5016_coveragepositioncriteria_erythropoiesis_stimulating_agents.pdf

"Pegfilgrastim"—https://static.cigna.com/assets/chcp/pdf/coveragePolicies/pharmacy/ph_5016_coveragepositioncriteria_erythropoiesis_stimulating_agents.pdf

"Preferred Specialty Management Colony Stimulating Factors - Filgrastim Products"– https://static.cigna.com/assets/chcp/pdf/coveragePolicies/NPF/npf_260_coveragepositioncriteria_colony_stimulating_factors_filgrastim_products_psm.pdf

"Infliximab"—https://static.cigna.com/assets/chcp/pdf/coveragePolicies/pharmacy/m_0003_coveragepositioncriteria_infliximab.pdf

"Oncology Medications" – https://static.cigna.com/assets/chcp/pdf/coveragePolicies/pharmacy/ph_1403_coveragepositioncriteria_oncology.pdf

towards aggressive substitution. There could have been varied causes for that direction, including a lack of understanding of biosimilar products, a reluctance to create coverage policy, or a deference to provider decision-making about biosimilars, or other reasons, perhaps related to pricing or uncertainty about managing this new type of product. PBMs seem to have been more likely to take an aggressive stand, perhaps because their perspective on drug markets is different than insurers.

Key Relationships for Biologic Markets

Sponsors of biologic reference products conduct the initial research and incur costs not only to develop the product, but also to create utilization, pricing, and product positioning for the reference biologic over the years it held sole positioning in the market. The commercialization of a biosimilar is affected by the dynamics already in place for that biologic, including the demand of the disease burden. Biosimilars will only succeed commercially for their developer if they can gain market share away from the reference product. The biosimilar manufacturer enters a mature market and navigates within the constructs of the relationships already established by the reference product.

These relationships encompass pricing, established comfort with the reference product related to trust and confidence in the manufacturer, patient experience, and real-world performance of the product in the treatment plan, contracts, rebates, distribution, inventory management, formularies, and top of mind awareness, not to mention operational details such as clinical treatment protocols, coding and pricing embedded in technology, forms, and editing processes.

Projections for the Biosimilars Market

There has been an evolution of thinking and expectations regarding the potential of biosimilar products. Before the first biosimilars were approved in the U.S., general expectations included hope that the potential financial pricing variation between the biosimilar and the reference products would be substantial. As the biosimilar products were brought to the FDA for approval, and then to market, the realities of production and development costs, as well as the impact of legal challenges from reference products led to a lowering of the financial differences for pricing for providers, payers, and patients.

A 2017 Rand report reviewed the burgeoning biosimilars industry (at that time, three biosimilars were then available in the market in the U.S.). This Rand report estimated the cost savings potential of biosimilars to be a *"$54 billion reduction in direct spending on biologic drugs from 2017 to 2026, or about 3 percent of total estimated biologic spending over that ten-year period, with a range of $25 billion to $150 billion."* [38]

In a report released in January 2020, Bonnie Bain, global head of GlobalData Pharma, was optimistic about the *"potential for biosimilar medicines to gain a stronger foothold in the U.S. during 2020. "Even though the price differential between biosimilars and their branded counterparts is only around 15 to 30 percent, which is significantly less than the cost savings seen with the average generic drug, we still expect that biosimilars will start to contribute cost-savings in the U.S. in 2020. Uncertainty still exists for reimbursement, automatic substitution, competition from next-generation biologics and litigation, but the fact that insurers such as United Healthcare placed Amgen's biosimilar mAbs on the primary tier of its formulary bodes well for future biosimilars."* [39]

Market launches in recent years are projected to yield a faster uptake than earlier biosimilar launches. Two 2018 pegfilgrastim biosimilar launches captured 25 percent of the product market share in just over one year. The first bevacizumab biosimilar launched in late 2017 captured 10 percent of the bevacizumab market in just four months.[40] Scott Gottlieb, MD, former FDA Commissioner, noted on Twitter on December 5, 2019, that *"biosimilars are growing their market share and will lead to meaningful price erosion over time – with the more recent biosimilar launches showing a lot of success – reflecting perhaps the growing market sophistication of the biosimilar companies."* [41]

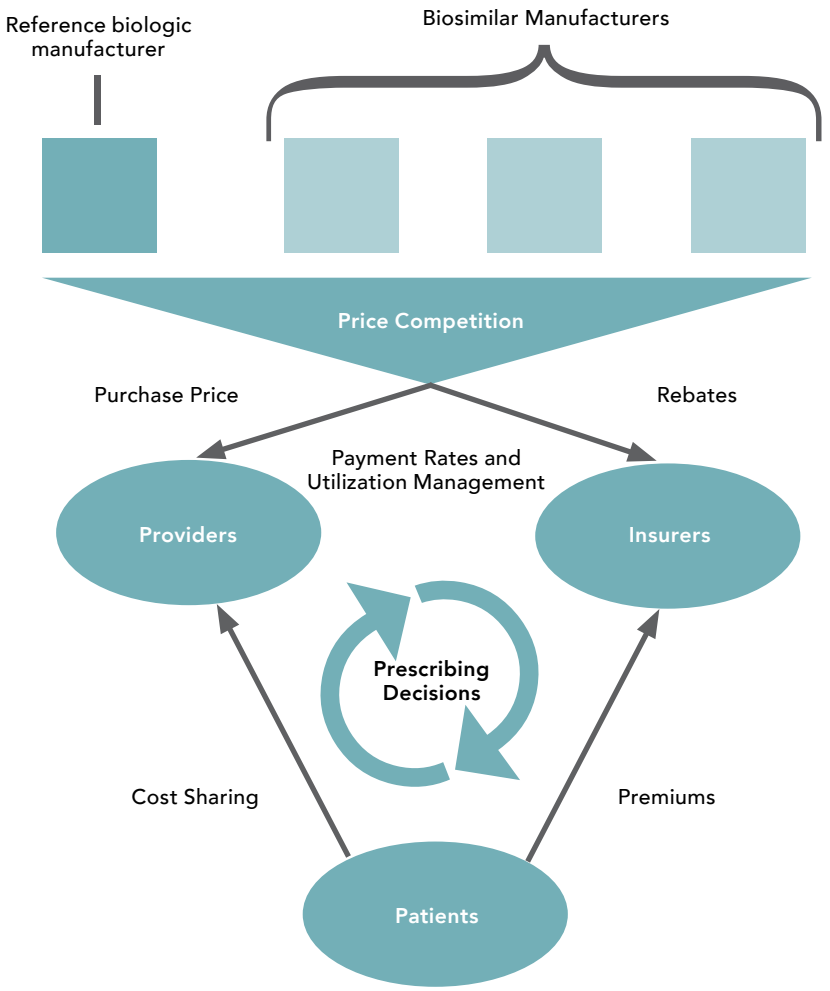
Key Drivers for Biosimilar Market Share Uptake

Any realization of potential savings will be a product of uptake and shifting of market share between the reference and biosimilar products. At the time of launch, the reference product holds 100 percent of the market share for that unique biologic. Uptake of the biologic product is heavily affected by industry, regulatory, provider, patient and insurer perspective and decisions, as well as any policy changes that could impact the biosimilar market.

RAND described the variables and relationships that come into play in a biologic market in 2017, which are represented in Exhibit 5. Those same relationships have affected the impact and uptake of biosimilars in the established U.S. biologic market since the approval of the first biosimilar.

As RAND describes the interactions, *"Biosimilars and their respective reference biologics are expected to compete on price to gain market share. Both insurers and providers are, in a way, buyers of biologics and can steer patients toward one product or another. Providers buy biologics from manufacturers or wholesalers and administer biologics to patients. Insurers influence prescribers by setting their own payment rates and through utilization management tools, such as prior*

Exhibit 5: Biologic Market Relationships As Defined by RAND



Source:

Mulcahy, AndrewW, Jakub P. Hlavka, and Sprncer R. Case, Biosimilar Cost Savings in the United States: Initial Experience and Future Potential. Santa Monica, CA: Rand Corporation, 2017. Last accessed on Dec.20, 2020 at https://www.rand.org/pubs/perspectives/PE264.html

authorization, which require prescribers to provide justification and documentation to support the insurer paying for a drug. Patients are also buyers of biologics to the extent that they pay for part of the cost of drugs through cost sharing. The manufacturer offering the best price to providers (including hospitals, physician practices, and pharmacies and the largest rebates to insurers should expect to gain market share and revenue. Over time, patients could benefit from lower out-of-pocket costs, and increased access to medications." [42]

PBMs should be added to that cycle, since in many cases, PBM vendors act as an intermediary for insurers, and in most cases requiring rebates for products placed on formulary. Biosimilar manufacturers face an extremely competitive playing field. Market share can only be achieved by another entity (provider, insurer, or patient) actively seeking to replace utilization of the reference product in an existing mature market with choice of the biosimilar. With many instances of multiple biosimilars vying against a common reference product, sales will likely be driven by price competition in addition to unique contracts and rebate arrangements. However, providers, payers (insurers, including PBMs) and patients have widely diverse reasons and options for choosing a specific drug. These key drivers can be in competition with each other, or complementary, which raises the complexity of entering the market, even after gaining FDA-approval.

Intellectual Property as a Key Market Driver for Biosimilars

Gaining FDA-approval as a biosimilar is just one step in the evolution of a biosimilar towards the open market. The originator (reference product manufacturer) is not likely to risk losing market share without attempting to protect the investment that they have made in the research, development, and marketing of the reference product. The BPCIA introduced specific procedures for resolving patent disputes between biosimilar and reference biologic manufacturers prior to the launch of a biosimilar. Incomplete notification and sharing of required information between the two manufacturers, or fear of the risk of patent litigation, can influence or delay the entry of some FDA-approved biosimilars into the market.[43]

Interchangeability (or lack thereof) as a Key Market Driver for Biosimilars

A natural inclination for an insurer or PBM seeking to reduce costs of care would be to look to biosimilars as a replacement for more costly biologics. In fact, as discussed earlier, some insurers and PBMs have changed their formularies to create preferred positioning for either a reference biologic or biosimilar, or some combination of the two. However, this is a complicated position since the FDA has not yet approved any biosimilar as "interchangeable" with its reference product. Additionally, the interchangeability guidance was not finalized until May 2019 and the FDA has since put out separate draft guidance for insulins where the requirement for interchangeability may be simplified.[44] Some biosimilars received FDA-approval before the FDA released guidance on the process of requesting interchangeability and their manufacturers have not made the decision to seek the new standing. All biosimilars to date have focused primarily on the medical benefit, which may make the regulatory designation of interchangeability mostly irrelevant.

The prescribing physician must identify a specific drug (biosimilar or reference product) by name when writing the prescription for treatment. Without an FDA interchangeability designation, pharmacists are not allowed to replace that specific drug with another without physician permission. If there ever is an FDA-approved product with an interchangeability designation, because it pertains to automatic pharmacy substitution, it would likely have little or no impact on medical benefit products, and would only affect retail or specialty pharmacy products, where there could be a possibility that a pharmacist might initiate an interchangeability substitution.[45]

"Switching" between Biosimilars and Reference Products or Other Biosimilars

The potential for substitution may lead to consideration of whether alternating between products (whether one or multiple biosimilars with each other or the reference product) can be allowed to happen for a given patient, particularly over a long course of therapy. To date, no consensus exists among stakeholders about switching patients between reference biological products and biosimilars, which may have been curbing the implementation of biosimilars in clinical practice. In a review of 178 studies in which switch outcomes from a reference product to a biosimilar were reported, data was derived from both randomized controlled trials and real-world evidence. Despite the limitations stemming from a lack of a robust design for most of the studies, the available switching data do not indicate that switching from a reference product to a biosimilar is associated with any major efficacy, safety, or immunogenicity issues. Some open-label and observational studies reported increased discontinuation rates after switching, which were mainly attributed to nocebo effects. The nocebo effect is characterized by negative responses to active treatments stemming from patients' negative expectations rather than the known pharmacologic action of the treatment itself.[46] This effect may lead patients to report symptoms, discontinue treatment, or to feel worse for reasons unrelated to the specific healing properties of the treatment. Nocebo effects can cause patients to drop out of clinical trials, stop taking drugs they need, or end up using other drugs that complicate their treatment.[47] Involvement of the prescriber in any decision to switch should remain, and attention should be paid to the mitigation of a potential nocebo effect.[48]

Reviews of switching studies have consistently shown a lack of data to justify suggested safety concerns, supporting the FDA contention that switching from reference products to biosimilars is safe and effective.[49] Biosimilar-to-biosimilar switching data is limited but growing. A recent study presented in October 2020 from the U.S. Veterans Affairs system demonstrated an 83 percent continuation rate among patients who were switched from either the reference infliximab or an infliximab biosimilar to another infliximab biosimilar using real-world switching data. Since the medical symptoms from inflammatory bowel disease can be severe, maintaining a stable condition is important for disease management. This study showed that patients can remain stable after switching to a biosimilar from either the reference product or another biosimilar without major safety concerns.[50]

State Laws as a Key Market Driver for Biosimilars

It is uniformly accepted that physicians have the right to prescribe whatever therapy they believe is most appropriate for their patients. State laws regarding pharmacist-initiated substitution of a biosimilar for a reference product are largely consistent but can vary in some respects. Since 2013 (even before the first FDA-approval of a biosimilar), states have been trying to clarify in law and regulations how and when a pharmacist can substitute a biosimilar for a reference biological product that has been prescribed by a treating physician. In general, most pharmacist substitutions are permitted under certain conditions if firstly, the drugs are therapeutically equivalent, if secondly, the substituted drug is less expensive, and lastly, if the prescriber has not precluded substitution by noting so on the prescription.[51] As of May 21, 2016, 21 states had passed laws on pharmacist substitution of biosimilars. By December 2020, 49 states and Puerto Rico had signed into law pharmacy regulation updates with biosimilar substitution language.[52,53]

State provisions could include specific language related to[54]

- Interchangeability – this language is usually still aligned with the FDA definition, with the FDA-approval and designation as interchangeable.
- Providers override of substitution – the prescribing provider may prevent a substitution, usually by writing on the prescription terms such as "do not substitute," "dispense as written," or "brand medically necessary."
- Provider notification requirements after the switch is made – specific states may require the prescribing provider to be notified of a substitution after an interchangeable biologic is dispensed to a patient in place of a reference product that had been prescribed, typically within five days of dispensing.
- Consistent with generic switches, the patient or patient's representative is to be notified of the switch. Requirements may also include notification to the patient or patient's representative, possibly with consent to the substitution.
- Records of the allowed substitution are retained by the pharmacies and prescribers for periods of time that can vary from state to state.
- Link to FDA-approved substitutions – many state biosimilar laws require the State Board of Pharmacy or some other state entity to maintain a link to the website listing of FDA-approved substitutions.

Provider Payment Rates as a Key Market Driver for Biosimilars

Medicare pays for drugs administered in a provider's office at a set federal rate based upon average selling price, net of discounts and rebates, plus a fixed percentage above. In recent years, that drug payment has universally been reduced by 2 percent because of the federal sequestration program. This payment methodology would lead to a financial penalty for providers who chose to prescribe a lower-cost biosimilar drug instead of the higher-cost reference product, an unintended disincentive for Medicare, which is trying to encourage utilization of biosimilar products. To protect providers from that unintended penalty, the BPCIA requires Medicare payment for biosimilars to include a fixed percentage based on the more-expensive reference biologic. The Medicare payment policy as of 2020 for biosimilars pays the calculated average sales price (ASP) for each individual biosimilar, plus the fixed percentage of the more expensive reference drug upon which that biosimilar was based.[55]

Clinical Guidelines as a Key Market Driver for Biosimilars

For any oncology drug, mainstream acceptance by providers and payers relies on positioning in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®). In May 2020, a NCCN steering committee voted unanimously to revise all its guidelines to indicate that an FDA-approved biosimilar is an "appropriate substitution" for a brand-name biologic as a treatment choice. The choice of words "appropriate substitution" does not mean that the drugs are to be considered interchangeable by a pharmacist but that physicians should consider biosimilars as viable treatment options in place of reference products. Real-world data is being collected for biosimilars as they enter clinical practice to evaluate their equivalency to their reference products.

The NCCN does not have a specific policy about whether clinicians should tell patients whether they are prescribing a biosimilar instead of a brand-name reference product, but the NCCN does have general recommendations that clinicians, in dealing with patients, be fully transparent.[56]

Real World Experience for Biosimilars – Provider Perspectives

The provider perspective on biosimilars lies at

the heart of the challenge for the slow uptake of biosimilars. Some and perhaps many physicians are inherently slow to adopt new products. Manufacturers dedicate significant resources to education and dissemination of information on clinical evidence, utility, toxicity, and insurer coverage for providers. That is a difficult enough process for a new product, but for a product seeking to gain market share for treatments and indications for which there is already an established branded product, and that physicians are comfortable using, the challenge is even greater.

Uncertainty – With no designated interchangeability, providers appear uncertain about prescribing biosimilars. Three years following the first approved biosimilar in the U.S., *"a 2018 survey from PricewaterhouseCoopers' Health Research Institute reported that 55 percent of clinicians reported being unfamiliar with biosimilars and more than one-third, (35%), reported never prescribing biosimilars. Another study conducted in 2016 found that 30 percent of physicians would not prescribe a biosimilar to a treatment-naïve patient, assuming similar efficacy and given their current state of knowledge. Barriers to prescribing biosimilars among hematologists and oncologists seem to include mistrust, issues with manufacture, and insufficient data. Education is considered key to improving understanding of biosimilar products. The American Society of Clinical Oncology (ASCO) noted in a 2018 statement that continuous provider education on biosimilars is "critical to inform, promote, and use biosimilar products in a medically appropriate and cost-effective way to treat cancer." Such education, according to ASCO, may include webcasts, online practice guidelines, social media updates, and educational sessions at scientific meetings."* [57]

Many challenges and considerations – Physicians consider a wide scope of issues when choosing a treatment for a given patient, as well as the drugs that they prefer to maintain in their inventory.

- Operational and quality issues arise regarding accessibility to a product from their preferred drug wholesaler with whom they have established a prolonged trusting relationship for on-time delivery, safe delivery within the requirements of each drug, pricing and volume contracts, and service for emergencies, including disruptive events such as weather or shortages.

Exhibit 6: Main Barriers to Biosimilar Adoption

Three suggested categories of barriers to biosimilar adoption, and common evaluative questions are: clinical, operational, and economical. These could apply to all potential consumers, including physicians, insurers, and patients.

Clinical

Safety and efficacy are always top of mind when it comes to pharmaceuticals, and biosimilars are no exceptions.
Potential clinical questions can include:

- What is a biosimilar?
- Is the biosimilar as effective as the reference product? Is it safe to switch from brand to biosimilar?
- Is the biosimilar approved for all the same indications?
- Who is the manufacturer?
- Are there patient support resources?

Operational

Products that are harder to use than other options will be less widely accepted.
Regarding biosimilars, practices may ask:

- Which payers cover this biosimilar?
- Do patients need prior authorization?
- Does the biosimilar manufacturer offer patient benefits investigation support?
- Does the biosimilar manufacturer offer patient support services like financial assistance/co-pay support?
- How do I submit biosimilar reimbursement claims to Medicare?
- Will there be additional requirements for tracking and monitoring patient utilization and impact of use of biosimilars compared to the standard requirements for the reference product?

Economical

- How will my reimbursement amount change over time?
- Will there be delays in coverage or reimbursement?
- How will reimbursement compare with changes in purchasing costs?

Source:

Amy Bigbee, Tommy Pourmahram, Omar Hafez, "Navigating biosimilar reimbursement: Key challenges and steps to success", MedCity News, Published online Apr. 24, 2020, last accessed Dec. 20, 2020 at https://medcitynews.com/2020/04/navigating-biosimilar-reimbursement-key-challenges-and-steps-to-success/?rf=1

- Operational challenges related to introduction of a new product to electronic health records (EHR). A practice may have preformatted EHR pathways that might require a modification or formal review process before new products can be added.

- Financial challenges may arise for providers, should insurance contracts reimburse reference products more or less favorably than biosimilars.

- Contracting issues may arise with the wholesalers and manufacturers from whom the providers traditionally procure their drugs. Existing contracts and pricing may be dependent upon volume commitments that may preclude switching to a different product (be it a biosimilar or a reference version of a drug).

- Clinical treatment protocols for medical decision-making are often looked at as guidelines for decision support and lack of inclusion of a specific drug can be significant.

- The burden of documentation, tracking and support services on the practice clinical team can be a real concern for uptake of a new product.

- Insurer coverage and reimbursement policies and rates will impact practices' costs and financial stability should the acquisition and handling burden of a specific drug exceed the potential for timely reimbursement.

- Another consideration for the physician is the need to educate and assure patients about the financial impact, role, safety, and efficacy of a biosimilar relative to the reference product – a particular challenge if the physicians themselves are not fully knowledgeable of those answers.

Multiple products are not manageable – Physicians face inventory and space limitations for their drug inventory. Stocking one reference product has been the standard. When biosimilars started to launch, another decision that providers had to address was what products they could afford to stock. Providers often do not have the physical space to carry an inventory of multiple biosimilars and the reference product for use depending upon the patient's disease requirements and different payer formularies.

Real World Experience for Biosimilars – Payer Perspectives

In many ways, the experience of watching the evolution of biosimilars in the U.S. has been frustrating for payers. For years, there were discussions of significant cost reductions, and then as the biosimilar launches began, those cost reductions fell into a less exciting range of below 30 percent, 20 percent, even 15 percent. Reluctant to aggressively force the hand of physicians early in the process, many payers waited and watched as physicians themselves delayed major uptake of the new biosimilars. Since the newly launched biosimilars were somewhat lower in cost than the reference products, payers did begin to cover them, but not to the exclusion of the reference product, which was often still utilized by most providers.

Support for Biosimilars needed – In April 2020, America's Health Insurance Plans (AHIP) felt it appropriate on behalf of its member insurers to recommend further actions to the FDA and FTC to streamline the biosimilar approval process and

Exhibit 7: Key Considerations for Payers for Evaluating Biosimilar Uptake

Key Considerations	Supporting Points
Clinical	Safety Efficacy Immunogenicity
Supplier	Knowledge of Manufacturer History of on time production and delivery Patient support services Payer and provider resources
Administration	Delivery system (pens, vials) Dosage options Storage requirements
Costs	List price Rebates Value-based agreements Reimbursement methodology (Average Selling Price versus Wholesale Acquisition Cost) 340b Medicare program impact Line of business
Operations	Prior authorization Formulary placement New starts versus stable patients Communication Medical versus Pharmacy benefit Interchangeability/substitutability

Source:

Benjamin P. Falit, Surya February 20, 2021. Singh and Troyen A. Brennan, "Biosimilar Competition in the United States: Statutory Incentives, Payers and Pharmacy Benefit Managers". Health Affairs, Published Feb. 15, 2015, last accessed Jan. 27, 2020 at https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2014.0482

to adopt other strategies to promote biosimilars and lower healthcare spending. The AHIP concerns included taking stronger actions against misinformation and anti-competitive practices regarding biosimilars, educating providers and patients about them, and supporting federal and state policies that promote access to biosimilars.[58]

Payer/PBM mechanisms to encourage biosimilar use – By mid-2017, payers were starting to place launched biosimilars on preferred brand tiers (which reduces out-of-pocket costs for patients compared to drugs on non-preferred brand or specialty tiers). Coverage of the biosimilar was usually in addition to coverage of the reference brand drug, not as a replacement. During these early months, payers were less aggressive about forcing providers and patients toward one over the other. Although insurers can often seek rebates for steering prescription volume to certain products, that willingness to switch from a reference product to a biosimilar may not be as strong.[59]

Non-Price Competition from reference biologic manufacturers – Reference biologics manufacturers are already developing next-generation biologics or add-on services that could offer improvements over their original reference biologic, as well as any biosimilars tied to that older reference product. This could mitigate or eliminate any anticipated savings from conversion to biosimilar market share.[60]

Gradual market share penetration, despite coverage of biosimilar and reference products – Coverage and market share can vary from one biosimilar to the next. Within two years of launch of the first biosimilar for filgrastim, that product was covered by 94 percent of employer-sponsored insurance plans. Over 40 percent of those plans covered the biosimilar in the preferred brand tier. In contrast, after seven months on the market, less than half (42%) of employer plans were covering the first launched infliximab biosimilar.[61] More recent biosimilar launches have been more successful in quickly garnering coverage and market share.

PRACTICAL USE OF BIOSIMILARS

The most obvious reasons for the creation of biosimilar products are access and financial impact. Biologic drugs are a valuable innovation. Cancer treatment by targeted biologics can lead to significant improvement and survival in both metastatic and early disease but, like many innovations, comes at a high cost. The biosimilar product receives designation as "highly similar" to a reference product, if it has the goal of greater access to critical drugs for patients, who otherwise may not have received biologics, as well as possible cost-effective alternatives and introduces price competition.

Competitive Factors Affecting Biosimilars

Increased competition can be complex in the biosimilars market. Traditional market patterns would result in prices of reference products sloping downward in the face of competition from one or multiple biosimilars. The following tales of two different biosimilar markets illustrate the variations that could occur in the healthcare marketplace, which will affect providers and payers, for pricing, access, and patient financial burden as well.

Variation 1 – Loss of reference product market share – The reference product trastuzumab, has five biosimilar competitors, four of which are already in the market as of December 17, 2020, with one other not likely to be brought to market. The reference product rituximab has two biosimilar competitors currently in the market, with another planned to launch in 2021. In Europe, a surge of biosimilars entering the market in 2018 resulted in aggressive discounting, and the reference product lost 30 percent of its market share in the next year.[62]

Variation 2 – Reference product held market share – A low number of biosimilar competitors led to a different story for infliximab. The first infliximab biosimilar was launched in mid-2016, followed by a second biosimilar infliximab in mid-2017, and another that has not yet launched is likely to not launch at all. GlobalData interviewed payers that noted that the limited number of biosimilar products available for this reference product stymied competition amongst the biosimilars and allowed the reference product manufacturer to renegotiate contracting agreements with insurers to match or beat the biosimilar price.[63]

Other variables – The administration method for infliximab may also have contributed to the impact on market share. As an infusion product, infliximab is priced lower than the subcutaneous adalimumab to compensate for the infusion costs. Because of the lower price point of infliximab, there may be less flexibility in the pricing margins for discounting than there are for adalimumab. Additionally, the massive size of the adalimumab market may make it easier for biosimilar developers to discount their prices competitively and still generate a margin over their costs.[64] Manufacturers of reference products may also bundle the rebate for their product with rebates for other drugs that they market, potentially forcing payers to decide whether to accept biosimilars, or risk forgoing rebates on the entire bundled product portfolio.

Dosage variables – The reference product adalimumab is available in a wide range of doses for different types of patients, including 10 mg, 20 mg, and 80 mg. Based upon current FDA labeling,

only a few of the biosimilar products are available at 10 mg and 20 mg pens/syringes and none are available at 80 mg. The convenience for providers and patients of the larger pen/syringe size, even for a small number of patients, may prove an edge for the reference product to retain market share.[65]

Other potential protections – Newer formulation changes and orphan drug exclusivity in the reference product could also reduce erosion in market share to biosimilars. The reference product for adalimumab is seeing patient demand shift volume to a new formulation with significantly less injection site pain. This could be an advantage for the reference product if the biosimilars do not also have the same formulation but would not be an issue if both reference and biosimilar adalimumab have similar formulations.[66]

Challenges for the Adoption of Biosimilars – Competing Perspectives

Biosimilar Disparagement and Misinformation

Biosimilars are a novel introduction to established reference product markets. The uptake has been slower than some might have expected. There has been discussion in the market regarding the potential for biosimilar disparagement and misinformation that may have affected understanding and use of biosimilars in some settings, whether intentional or otherwise. Co-chairs of the Education Committee of the Biosimilars Forum suggested that there are several different types of disparagement and misinformation directed towards biosimilars as a class, including:

- *"Statements about biosimilar science or policy that are factually incorrect.*
- *Misleading information, where the information is correct, but is provided out of context.*
- *Incomplete information, where only partial or a limited set of facts are provided.*
- *Creation of a false narrative, especially in scientific and medical literature, which provides a set of references to support incorrect conclusions.*
- *Negative message framing of factual statements to create a negative perception."*

These authors suggested that *"disparagement and misinformation about biosimilars can be countered by educational efforts, appropriate oversight, and regulatory activities with the option of enforcement action by governmental agencies, if warranted."* [67] As with any new product, managed care medical directors, physicians, nurses, pharmacists, and patients deserve access to evidence-based, balanced educational materials.

There are few direct incentives for physicians to convert to biosimilars without insurer contract modifications – Though value-based contracts are often discussed, few contracts between payers and providers provide incentives (such as scoring, reimbursement, population management, accountable care, or patient impact) that would offset the potential losses that providers might incur from a conversion to a biosimilar from the reference product. Under a traditional buy and bill system, the physician buys the inventory of the drugs needed for the upcoming week for patients (some known in advance due to scheduled treatments, and some based upon trends in practice treatment patterns). The costs for this inventory are charged almost immediately by the drug wholesaler and paid immediately to take advantage of cash payment discounts. The physician then treats the patient, submits the claim for reimbursement, and waits days, weeks, even months, to receive that reimbursement, which may or may not be above the acquisition cost for the drugs. Without value-based contracting that recognizes in some financial manner the efforts of a physician to manage the total costs of care for a patient (assuming that a biosimilar product is an appropriate option) the treating provider may well lose money each time they prescribe a lower margin biosimilar versus a reference product.

A 2017 Navigant study determined that for a *"hypothetical infused reference product, which cost $1,000 per unit dose, and a biosimilar priced at a 15 percent discount, an average physician's office would lose $9 in gross margin per dose; outpatient hospitals could lose $43 per dose, and 340B or disproportionate share hospitals could lose up to $79 per dose. Individual providers with 50 eligible patients on therapy could lose up to $50,000 per year, losses that would magnify as more biosimilars launched in the market…A single biosimilar product such as infliximab, which was used to treat over 130,000 Americans in 2016 could decrease margins by as much as $100 million across providers. Commercial payers could follow the lead of Medicare in developing value-based models (like the Oncology Care Model) that offer favorable and differential reimbursement for providers that adopt biosimilars."* [68]

It is worth noting that this study was conducted prior to the Medicare changes of 2018 where blended rates were replaced by individual ASP pricing plus a percentage of the reference product ASP rate for physician providers and non 340B status hospitals. As

a result of those 2018 changes, biosimilars are treated as reference products and are accorded "pass-through status" under Medicare 340B policy, which means, that 340B status hospitals are reimbursed at the rate of ASP plus 6 percent rather than ASP minus 22.5 percent (which applies to the older, reference products for the biosimilar). This policy provides potentially higher payments for those hospitals using pass-through status biosimilars instead of reference products.[69]

Value based models – Oncology Care Model a moderate driver – Biosimilars might reduce the costs of treatment for patients and payers, however, providers, who have been left to rely on drug margins to offset underpaid costs of cancer center operations, are unlikely to choose to switch to biosimilars and reduce those margins and jeopardize the financial stability of their practice. Those practices participating in the Medicare Oncology Care Model program (which started in 2016 and was extended due to the Corona Virus pandemic until July 2022) do have an incentive to reduce the total costs of care to Medicare and have shown a faster uptake of biosimilars than practices that do not participate in the program. This program is scheduled to end soon, and the impact of that program ending (depending upon what type of program Medicare may develop next) could influence the rate of biosimilar uptake in over 150 practices and cancer programs.

Implications of Federal Actions for the Biosimilars Market

The Oncology Care Model and Biosimilars

In 2016, Medicare enrolled almost 200 provider groups into a new oncology payment program. This five-year pilot value-based program sets baseline, severity and new technology adjusted target rates, and assesses the provider groups' performance in six-month periods against the target for total costs of care for the designated beneficiaries. In addition, Medicare pays a monthly disease management type fee per beneficiary to offset the costs of program compliance. The target-based performance is adjusted against paid disease management fees, and participating provider groups participate in any total population savings on a percentage driven by quality measure performance.

It was interesting to watch the provider groups evolve during the program toward population management. After focusing on external cost drivers such as hospitalizations, repeat admissions and emergency room visits, they began to turn attention to treatment and drug choices. Biosimilar uptake became a natural option for many participating groups. A 15 to 20 percent reduction in the total costs of some biologics became an attractive target for savings. This developed because the total OCM payment program was structured with a combination of disease management payments as well as quality performance driven savings bonuses, but it is important to note that the structure of the OCM payment program provided a platform against which providers felt safe looking at the potential of biosimilar products.

A 2018 study by a participating OCM oncology practice looked at average Medicare reimbursement for pegfilgrastim from July 1, 2016 through June 30, 2019. They compared the average reimbursement and the average change in reimbursement before and after the introduction of biosimilars. The conclusions were that *"in 2018, 88,847 Medicare patients received pegfilgrastim, resulting in $1.39 billion in Medicare reimbursement. If the pattern they detected in our OCM data sample could be applied to the general Medicare population, during the fourth quarter of 2018, they estimated that the introduction of biosimilars would have resulted in a $4.8 million savings (1.39%) compared with what the total reimbursement would have been without biosimilars in the market. This bending of the cost curve is projected to result in savings of $79.1 million (5.6%) in 2019 and $157.9 million (11.5%) in 2020. Importantly, most of this cost containment is not due to patients utilizing biosimilars. In the second quarter of 2019, 90.6 percent of patients were still receiving branded pegfilgrastim. However, the introduction of biosimilars has caused even the branded agent to stabilize and possibly drop net acquisition prices."* [70]

Early evaluation of the OCM program reflects an increase in the use of some biosimilars by OCM participating practices. Measurements of the OCM program in the first 18 months of the five-year program (performance periods 1, 2 and 3 between July 1, 2016 and June 30, 2017) showed more than a 20-percentage point impact on the use of the biosimilar filgrastim versus the reference product for each of three cancer types (Breast, Lung and Colorectal) studied. This was ultimately expected to reduce Medicare costs for beneficiary care.[71]

The Affordable Care Act and Biosimilars

The 2010 Affordable Care Act (ACA) has been under review and discussion since its inception. Throughout the administration of President Trump, several initiatives were raised to reduce or repeal this Act. Some of these initiatives have reached the level of the U.S. Supreme Court and are under review. One of these, is the decision by the U.S. Supreme Court to hear California versus Texas, a case that will decide whether most or all of the ACA should be overturned, based on the question of the

constitutionality of the ACA following the passage of the Tax Cuts and Jobs Act of 2017.

This case, which is still pending, could affect the biosimilars market because the Biologics Price Competition and Innovation Act (BPCI) is embedded within the ACA. The BPCIA created the regulatory pathway for biosimilars, and marked the beginning of a new era for biologic treatments in the U.S. The first biosimilar was introduced in 2015 and saved the health care system nearly $500 million in less than two years. For every treatment with an on-market biosimilar, the average selling price of reference medicines declines annually by about 9 percent. *"If the U.S. Supreme Court were to overturn most, or all, of the ACA, the regulatory pathway for biosimilars could disappear, causing significant disruption for the development, approval, and marketing of new biosimilar versions of biologic treatments."* [72] The Supreme Court also has the option of upholding the ACA completely, or severing the BPCIA from aspects of the ACA that could then be struck down. Under these last two scenarios, the biosimilar pathway would not be impacted. A Supreme Court decision is anticipated in mid-2021.

Observations from Other Entities Regarding Biosimilar Policy Moving Forward

Highlights of Biosimilars as a new standard for value care are:

1. Biosimilars are not generics – Biosimilars are biologics that are *highly similar* to, and have no clinically meaningful differences from, FDA-approved reference products.[73]

2. *"While it can cost about $5 to 10 million to develop a generic version of a small molecule drug, the complexity of manufacturing and testing biosimilars currently requires much more significant outlays by biosimilar sponsors, costing typically, $100 million to $250 million per program."* [74]

3. Biosimilars would allow *"1.2 million more U.S. patients to gain access to biologics by 2025. Women, lower income, and elderly people would disproportionately benefit from access to biosimilar medicines."* [75]

4. Lower costs for biosimilars can reduce a patient's average out-of-pocket costs by 17 percent.[76]

5. *"On average, commercial insurers and state Medicaid programs can save tens of millions of dollars a year by simply expanding biosimilars' market share for the nine drug classes examined. Importantly, these potential savings exist in every state."* [77]

6. Biosimilars will reduce direct spending on biologics by $54 billion from 2017 to 2026.[78]

7. *"The Congressional Budget Office estimates that the sales-weighted market average discount on biosimilars would be 20 to 25 percent relative to reference agents."* [79]

8. These FDA reasons are why biosimilars are just as safe and effective as the original biologic:
   a. *"Approving of biosimilars after a careful review of data, studies, and tests.*
   b. *Monitoring safety and effectiveness after approval.*
   c. *Checking for medication quality during production.*
   d. *Reviewing patient safety reports made to the FDA."* [80]

NCCN Guidance on Biosimilars in Oncology

In March 2011, an NCCN work group published guidance regarding the challenges that health care providers and other key stakeholders face in incorporating biosimilars into health care practice. The resulting white paper addressed health care provider knowledge, substitution practices, pharmacovigilance, naming and product tracking, coverage and reimbursement, use in off-label settings, and data requirements for approval.[81] By 2020, NCCN's senior vice president and chief medical officer Wi-Jin Koh, MD, noted that an *"NCCN steering committee voted unanimously in May 2020 to revise all of its NCCN Clinical Guidelines to indicate that an FDA-approved biosimilar is an "appropriate substitution" for a brand-name biologic."* [82]

ASCO Education and Guidance on Biosimilars in Oncology

In a formal published 2018 statement, ASCO offered education and guidance on the safety and efficacy of biosimilars in the cancer setting. This ASCO guidance covered:

- safety and efficacy
- interchangeability, switching and substitution
- naming labeling and other regulatory considerations
- the value of biosimilars
- prescriber and patient education.

In this guidance, ASCO recognized that *"Medicare, Medicaid, and commercial payers all have approached the reimbursement of biosimilars differently; however, it is clear that reasonable compensation, fair and medically appropriate coverage, and transparency of cost will serve to ensure a true value benefit to patients and society and promote access to new and innovative therapies."* [83]

Recommendations from the Hematology/Oncology Pharmacy Association on Biosimilars

The Hematology/Oncology Pharmacy Association (HOPA) first issued a brief on biosimilars in 2014, which was revised in 2015, and then updated in 2019. HOPA feels strongly that *"individuals with cancer should have access to biologic medications that offer significant advances in the treatment and cure of cancer. Biosimilars have the potential to increase access to life-saving therapy by reducing the financial barriers that exist for many of the current high-cost cancer therapies. HOPA makes the following recommendations to ensure appropriate access to, and safe use of, biosimilars.*

- *Support elimination of manufacturer rebate incentives with payers and PBM's that restrict access to biosimilars. This restricted access inhibits provider decision making regarding patient access to lower cost treatments for patients and increases patient financial toxicity.*
- *Support parity access to all biosimilars with third-party payers which would eliminate a preferred product preference of one biosimilar product within a class. The result of which would eliminate undue administrative, financial, and legal liabilities due to increased inventory management complexity.*
- *Promote education regarding the scientific, regulatory, pharmacovigilance, and practice implications regarding biosimilars. This information should be provided to all healthcare stakeholders, but especially providers, payers, and patients.*
- *Infrastructure should be improved to facilitate provider reporting and monitoring of any unique toxicities of all biological drugs observed after approval.*
- *Future biosimilar substitution legislation should be developed with input from State Boards of Pharmacy, local pharmacy organizations, and healthcare providers. Key parameters within current law regarding generic substitution should be a basis for the legislative discussion."* [84]

ISOPP Global Position on the use of Biosimilars in Cancer Treatment and Supportive Care

The International Society of Oncology Pharmacy Practitioners convened a Biosimilars Taskforce to provide the global oncology pharmacy community with guidance to support decisions around biosimilar use. Their 11 statements cover *"the regulation and evaluation of biosimilars, practical issues around local implementation, the education of healthcare staff and patients, and the requirement for ongoing pharmacovigilance and outcome monitoring.*

- *Statement 1: A biosimilar licensed via national or regional regulatory agencies requiring rigorous pathways for medicine manufacturing and evaluation is considered therapeutically equivalent to the originator biotherapeutic. However, a biosimilar is not considered therapeutically equivalent to other biosimilars of the same originator biotherapeutic.*
- *Statement 2: Biosimilars are not considered interchangeable with originator biotherapeutics and should not be automatically substituted. However, a switchover from an originator biotherapeutic to a biosimilar within institutions or for individual patients is acceptable and encouraged.*
- *Statement 3: Extrapolation of biosimilar data to all clinical indications may occur provided that enough relevant safety and efficacy data exist to support use.*
- *Statement 4: Differences between originator and biosimilar product formulations do not alter clinical efficacy but may enhance immunogenicity or intolerability risks. Inactive components should be reviewed for each biosimilar product before use.*
- *Statement 5: Partial implementation of a biosimilar, or institutional use of multiple biosimilars, may need to be considered as appropriate for the health care institution or patient populations served.*
- *Statement 6: Adherence to best practice guidelines on the storage and labeling of biosimilar products will reduce the risk of selection error. In the absence of best practice guidelines, universal naming guidelines should be applied to support biosimilar tracking and pharmacovigilance.*
- *Statement 7: Multidisciplinary groups should guide the safe, effective, and fiscally appropriate institutional use of biosimilars.*
- *Statement 8: Staff education on biosimilars should reference published, evidence-based, and peer-reviewed literature whenever possible. Educational materials should be updated and reviewed on an ongoing basis.*
- *Statement 9: Patients should be educated about biosimilars with resources that are evidence-based and tailored to patient demographics and health literacy. Such resources should be publicly available and adaptable to reflect the target population's needs.*
- *Statement 10: Institutional cost savings made using biosimilars should be used to keep patient costs manageable and to stabilize budgets to maximize the number of patients served.*

- *Statement 11: Pharmacovigilance and patient-outcome monitoring are integral to the safe and effective use of biosimilars in different populations and indications."* [85]

Suggestions from the Biosimilars Forum, a Biosimilar Trade Association Perspective

The uptake of biosimilars in other countries far outstrips that of the U.S. As of late November 2019, there were 54 biosimilars approved for use in Europe, almost all of which are already being marketed. In contrast, at the same time, the FDA in the U.S. has approved just under 30 biosimilars, only nine of which were actively being marketed. In late 2019, biosimilars made up less than 3 percent of the U.S. biologicals market. In 2019, 90 percent of global biosimilars sales took place in Europe, despite 60 percent of overall global biological sales occurring in the U.S. The President of the Biosimilars Forum, Ms. Juliana Reed, outlined a framework for improvement of the biosimilars market at the DIA Biosimilars Conference in September 2019.

In her presentation, Ms. Reed concludes that *"anti-competitive behaviors and other market and regulatory dynamics currently discourage market uptake of U.S. biosimilars including, misinformation, exclusionary contracting and rebate practices, limited reliance on global biosimilar experience and successes, patient litigation, and length of time from FDA-approval to market launch."* Her concern with this delayed market uptake is the impact on potential savings for patients and the U.S. She is not alone in these concerns, quoting *"Former FDA Commissioner Scott Gottlieb as stating that 'if Americans had the opportunity to purchase successfully marketed, FDA-approved biosimilar prescription drugs, they could have saved more than $4.5 billion in 2017.'"* [86]

Ms. Reed suggests that *"to obtain a sustainable and competitive biosimilars market for the Medicare program, and by extension to private insurers, the following criteria need to be met:*

- *Fair and early access to the market*
- *Appropriate pricing*
- *Biosimilars from several competitors on the market*
- *Broad insurance coverage*
- *Educated and supportive physicians and patients*

She believes that some measures have already been put into place to address anti-competitive behaviors, including:

- *The Trump administration signed bill requiring drug makers to send details of biosimilar deals to the Federal Trade Commission (FTC) for scrutiny.*

- *Senators Grassley and Klobuchar writing to FTC Chairman Simons urging the FTC to help end anti-competitive behaviors that hinder or delay market entry of biosimilars.*

- *The FDAs Biosimilar Action Plan stating that the FDA will coordinate with the FTC to address anticompetitive behavior.*

Ms. Reed also suggests that certain proactive policies could incentivize the uptake of biosimilars, including reducing out-of-pocket patient costs, shared savings with prescribers, and increasing an ASP add-on payment rate." [87]

Community Oncology Alliance Position Statement on Biosimilars in Oncology

Recognizing the rise in growth of both biologics and biosimilars, the Community Oncology Alliance issued its own position statement in April 2019 on the role of biosimilars in cancer care, which includes the following:

"Realization of the projected cost savings, however, will require that biosimilars are embraced and utilized. As more biosimilars become available after receiving regulatory approval, adoption in clinical practice is expected to increase, but this is currently in its infancy and much work remains. The results of a 2015 – 2016 survey led by the Biosimilars Forum show that major knowledge gaps about biosimilars and their potential use in clinical practice still exist among U.S. specialty physicians, including oncologists. Key gaps include:

- *defining biologics versus biosimilars in the context of biosimilarity.*

- *understanding the approval process and the use of the "totality of evidence" approach by the FDA for biosimilar evaluation.*

- *understanding the evidence requirements for demonstration of safety and immunogenicity of a biosimilar versus its reference product.*

- *understanding the rationale for indication extrapolation.*

- *defining interchangeability in the context of pharmacy-level substitution.*

As additional biosimilars are approved in the U.S. and awareness grows, it is anticipated that biosimilar uptake and utilization will increase subject to acceptance by the prescribers, payers, and patients. There is a need to educate multiple stakeholders, including physicians and other health care providers, about biosimilars, to raise awareness and increase utilization of these potentially cost-saving therapies. Patient education is also critical to increasing acceptance of biosimilars. Biosimilars will also play a key role in the success of value-based care models, such as the Oncology Care Model and the Medicare Shared Savings Program.

Community Oncology Alliance Position

COA is committed to working with the relevant public policy bodies (FDA, CMS, etc.), clinical organizations, professional associations, and advocacy groups, to support the acceptance of biosimilars across a range of sectors and bridge the knowledge gap in the key areas mentioned above. COA is also committed to working together with manufacturers of innovative biologics and biosimilars to reduce the cost of care, improve access, and reduce financial toxicities while continuing to provide logistical support for innovation in cancer treatment. With the intent of providing better access at affordable prices, reducing overall spending in Part B drug prices, and reducing financial toxicities experienced by patients, COA will work with all stakeholders to assimilate biosimilars and provide support to patients, physicians, and payers." [88]

EFFECTIVE PAYER STRATEGY FOR A HEALTHY BIOSIMILARS MARKET

Patients, providers, and payers deserve the benefits of a healthy biosimilars market. A collaborative strategy to achieve the potential for enhanced competition in a costly biologics market, safe evidence-based real-world clinical decision-making, access in a timely and cost-effective manner, will lead to responsible treatment choices and a natural evolution of biosimilar market uptake.

If payers wish to encourage and support the uptake of biosimilars where appropriate, there are a few potential areas on which strategic policy can be concentrated.

Formularies

Payers may want to evaluate the incorporation of biosimilars into formularies based on several factors, including product characteristics and evidence, knowledge of manufacturer, availability, dosage-form suitability for the covered population, patient adherence, and the economic impact on payers, providers, and patients. Education may be a factor for providers and patients when the patient is starting on a new regimen, and even more so for patients who are in the middle of their treatment and stable on their current medications. Individual biosimilars are approved based upon the totality of evidence, including extrapolated data, and are unlikely to have been formally evaluated against other biosimilars of the same reference product. Although each biosimilar demonstrates quality attributes that fall within the range established by the same reference product, treating providers may seek more information before transitioning from biosimilar to biosimilar. Further evaluation and consideration on a case-by-case basis may be necessary before considering alternating among biosimilars. While no problems have yet been observed, at present there is only a limited amount of real-world evidence evaluating biosimilar-to-biosimilar switching.[89]

Unintended Adverse Consequences of Payer Mandates

Payer mandates for one individual biosimilar may seem beneficial or convenient from the payer perspective but are highly likely to cause significant consequences for treating providers and patients. Because treating providers care for multiple patients with diverse insurance coverage, each payer mandate will increase the needed inventory and operating costs for that treating provider. They will also introduce patient safety concerns in terms of the correct individual payer mandated product being acquired, stored, pulled, prepared, and invoiced with appropriate safeguards. Allowing the provider to select and stock their preferred inventory choices will improve efficiency in care, safety in inventory and drug management, and enhance patient and provider comfort and familiarity with the product and thus quality of care.[90]

Economic Impact

Biosimilar markets are not like the generic markets. The expected cost reductions by biosimilars in the U.S. may range from 10 to 40 percent, but often less when generic drugs are introduced. While these reductions are lower than those expected for generic drugs, the overall magnitude may be greater in terms of absolute savings, due to the higher cost of the reference biologic products. Payers will likely still need to negotiate with manufacturers to achieve projected savings beyond the originator price adjustments.[91] One challenge will be to balance these manufacturer price negotiations with a sensitivity to the burden that unique payer requirements for one specific biosimilar will place on the provider, and the impracticality of a provider stocking multiple biosimilars to match different payer preferences. Involvement of PBMs with additional manufacturer negotiations and unique formularies will place a further unsustainable burden on the provider related to biosimilars.

An October 2019 study published by the Center for Medical Economics and Innovation at the Pacific Research Institute estimated national annual savings of over $240 million based upon utilization, as of February 2019, of biosimilars (about $47.5 million realized by state Medicaid programs and $136.8 million realized by the commercial market). This study then projected potential annual savings for the U.S. healthcare systems of nearly $7.0 billion, based an

assumption of biosimilar market share of 75 percent.[92]

Physician Payment

Until there are FDA-approved interchangeable products, the choice to use a biosimilar product over a reference product will remain in the hands of the prescribing physician. PBMs or others may place the biosimilar and reference product in varied positions on the formulary, however, a physician with a strong opinion will go through the necessary processes to ensure the patient receives the product version deemed most appropriate for their care. Insurers and employers would benefit from considering options like the Medicare payment policy of reimbursing biosimilars at their average selling price (ASP) plus 6 percent of the ASP of the reference biologic.[93] This calculation protects the treating provider from adverse financial consequences when choosing a biosimilar over a reference product.

Once a treating provider commits to using a biosimilar in place of a reference biologic, the next decision is to whether begin using it on all patients (new starts and patients receiving the reference biologic) versus using the biosimilar only in patients beginning therapy and/or just for certain indications. Some physicians may consider using biosimilars initially for new starts or select indications and then transition to all patients when appropriate.[94]

Patient Impact

Managed care organizations may have focused more education and discussions with providers, given that most biosimilars to date are administered under the medical benefit. As more biosimilars launch, that would fall under the pharmacy benefit, that may change. A such patients may not understand what a biosimilar is, or if it will have the same effect as the branded reference product they are already using, particularly since most biosimilars are administered intravenously in the treating provider's office. Also, patients with cancer may be more likely to be grandfathered into using reference products.[95]

Treating providers and their patients who are well-controlled on a reference biologic may hesitate to switch from the reference biologic to a biosimilar despite little evidence associated with increased risk of switching.[96] Patients with no copay differential, or a fixed copay, are more likely to choose a branded reference product if given multiple options, according to some patient advocacy organizations. Patients with a high-deductible plan, or with co-insurance where out-of-pocket expenses are calculated as a percentage of the drug's price are more likely to pursue use of biosimilars as an appropriate alternative to a more costly biologic.

"Patients for Biologics Safety and Access (PBSA) is a national coalition of more than 20 patient advocacy organizations that aims to ensure that the voices and interests of patients are heard, as the FDA considers approval of biosimilars. PBSA believes that patients must have access to safe and effective biologic medicines, including biosimilars, and all the information necessary to make a fully informed choice about which biologic to use." [97]

Value-based Payment Models

Payers may also wish to review the Medicare Oncology Care Model program as a potential role model, allowing treating providers to make the ultimate decisions regarding when and where to use biosimilars. The OCM has validated the axiom that a supportive provider payment program can incorporate disease management and attainable targets with quality-based performance opportunities. With such a collaborative program, part of the natural evolution of an engaged provider's knowledge, and some degree of accountability for total costs of care, is to review drug treatment choices and costs. Uptake of biosimilars becomes almost organic under that type of payment model. It does not penalize the physician as such choices could under a traditional fee-for-service system.

Value Beyond Price

"A payer's decision to adopt a biosimilar for formulary inclusion should be based on the quality and overall value as opposed to the price alone. Elements that also contribute to the value of a drug include, product quality established through extensive analytical and functional assessments during product development, provider-focused education, provider engagement, manufacturer support and resources, and additional services such as, anticounterfeit protection.

Manufacturing considerations, supply chain security, and logistics are also important when determining the relative value of a biosimilar. Physicians may develop a preference for biosimilars from manufacturers strong supply chain security, and counterfeit protection. It is also important to consider potential differences between delivery devices for biosimilars and reference products, which may provide added benefit to patients and health care providers.

As with generic medications, the reduced price of a biosimilar may also translate to other benefits in addition to cost savings. These may include improved medication adherence associated with lower copays, and enhanced motivation for reference and biosimilar manufacturers to invest in innovation to differentiate themselves in an increasingly competitive market." [98]

Neutral Policy

Neutrality related to choice and adoption of biosimilars by treating providers may be considered as a strategy for managed care at this time. The biosimilar market shows potential but is still evolving. The documentation requirements expected by the FDA to prove interchangeability are onerous and relatively few manufacturers are currently pursuing that option. Without an interchangeability designation, both providers and payers may be reluctant to accept biosimilars, irrespective of FDA messaging that patients and their healthcare providers can expect the same clinical outcomes as with use of the reference product. Many oncologists may have an aversion to changing products in the middle of a treatment cycle, or even to change products at all on a patient when the existing product appears to be well tolerated and efficacious for the patient. A neutral insurer policy would also recognize that the costs to providers of maintaining inventory to accommodate the "preferred" biosimilar of multiple insurers is cost prohibitive and not sustainable. Therefore, a neutral insurer policy would remain neutral as to which biosimilar product is used by the provider, and offer coverage across any biosimilar option, including the reference product. This strategy may diminish potential savings opportunities for the payer, patient, or healthcare provider.

Aggressive Policy

Some insurers and policymakers may choose to collaborate and intervene to guide the biosimilar market more rapidly to a sustainable, competitive state. The FDA could investigate options to provide stronger, earlier education on biosimilars, interchangeability and other topics. Insurers could pilot payment programs that encourage provider uptake without penalty. One option could be an expansion of current payments with the addition of a percentage or flat fee on top of the fixed percentage calculated from the reference biologic's ASP. Insurance or Medicare Part D policies might look to modifications to balance provider and patient incentives for uptake of biosimilars, including lowering or eliminating cost-sharing for use of biosimilars. Changes to Medicare programs often spur comparable changes in the private insurance market, so exploration of the work that the federal government has already done that has supported an uptake in the biosimilar market may be worth exploring.[99] Insurers could collaborate with providers and develop real-time monitoring of patients using biosimilars and create useable data sets to fuel evidence-driven policy for continued uptake of biosimilars.

SUMMARY

The U.S. market holds a wide variety of challenges and opportunities for incorporation of biosimilars. But there are many minefields to navigate. The FDA has created a pathway to approval, but significant hurdles exist beyond that approval. Beyond the already discussed litigation, regulatory and coverage obstacles, there are pricing and trust barriers to overcome from the payer's perspective as a steward of managed markets' clients and patients. Despite the past 10 years, there has been a slow uptake, with significant gaps in provider and patient education. Education and communication may be the two primary elements for biosimilar market strategy at this point. Pricing will always be a major factor in the consideration of the biosimilar versus the reference product. That is the primary difference between the two, but there are a host of other factors to balance.

Each payer should take the time to review the variables for managing a biosimilar strategy, and enjoy the benefits of innovation, ingenuity, development, and productivity that can be achieved. Effective management and adoption of a biosimilar strategy should yield savings to the insurer, the provider, the patient, the total cost of drugs, and to the entire health care system that can be applied to the future of health care.

Dawn Holcombe, MBA, FACMPE, ACHE, is President of DGH Consulting in South Windsor, CT, and Editor-in-Chief of Oncology Practice Management Journal. She serves as the Director for the NAMCP Medical Directors Institute Oncology Council and as the Executive Director of the Connecticut Oncology Association.

References

1. "Biosimilar and Interchangeable Products—What is a biological product?" web page, U.S. Food & Drug Administration web site, last accessed December. 15, 2020 at https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products
2. Ibid
3. Leigh Ann Anderson, PharmD, "What are Biosimilars? Top Facts You May Not Know" web page, Drugs.com web site, Last updated on Jul. 22, 2020, last accessed Dec. 3, 2020 at https://www.drugs.com/slideshow/biosimilars—1264
4. Mulcahy, Andrew W., Jakub P. Hlavka, and Spencer R. Case, Biosimilar Cost Savings in the United States: Initial Experience and Future Potential. Santa Monica, CA: RAND Corporation, 2017. Last accessed on Dec. 20, 2020 at https://www.rand.org/pubs/perspectives/PE264.html
5. Ibid, Mulcahy
6. Kashyap B. Patel, Juiz H. Arantes, Wing Yu Tang, and Selwyn Fung, "The role of biosimilars in value-based oncology care", Cancer Management and Research, 2018; 10: 4591-4602, last accessed Feb. 15, 2021 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6199968/
7. Ibid, Patel

8. "Biosimilar and Interchangeable Products—What does it mean to be "highly similar" and What does it mean to have "no clinically meaningful differences?" web page, U.S. Food & Drug Administration web site, last accessed Dec. 15, 2020 at https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products

9. Whitney Pittman, PharmD, Ashley Glode, PharmD, BCOP, Christina Wern, PharmD, "Review of Biosimilars and Their Potential Use in Oncology Treatment and Supportive Care in the United States," Journal of Hematology Oncology Pharmacy, Sept. 2019 Vol 9, No 3 - Review Article, last accessed on Dec. 10, 2020 at http://jhoponline.com/jhop-issue-archive/2019-issues/jhop-september-2019-vol-9-no-3/17837-review-of-biosimilars-and-their-potential-use-in-oncology-treatment-and-supportive-care-in-the-united-states

10. "Biosimilar and Interchangeable Biologics: More Treatment Choices" web page, U.S. Food and Drug Administration web site, Content current as of: Mar. 3, 2020, last accessed Nov. 11, 2020 at https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices

11. N.A. Nixon, MD, M.B. Hannourf, PhD., S. Verma, MD, "The evolution of biosimilars in oncology, with a focus on trastuzumab", Perspectives in Oncology, Current Oncology Volume 25, Supplement 1, June 2018, last accessed on Dec. 3, 2020 at https://www.current-oncology.com/index.php/oncology/article/view/3942/2762

12. Ibid, Pittman

13. Ibid,"Biosimilar and Interchangeable Products—What is a biological product?"

14. "Biosimilar and Interchangeable Biologics: More Treatment Choices" web page on the U.S. Food & Drug Administration web site, content current as of Mar. 23, 2020, last accessed Feb. 12, 2021 at https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices

15. Ibid,"Biosimilar and Interchangeable Products—What is a biological product?"

16. "Implementation of the Biologics Price Competition and Innovation Act of 2009", a web page on the U.S. Foo d & Drug Administration web site, content current as of Feb. 12, 2020, last accessed Dec 9, 2020 at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/implementation-biologics-price-competition-and-innovation-act-2009

17. Frank K Agbogbo, Dawn M. Ecker, Allison Farrand, et al, "Current Perspectives on biosimilars", Fermentation, Cell Culture and Bioengineering - Review, Journal of Industrial Microbiology & Biotechnology, 46. 1297-1311 (2019) Published July 17, 2019, last accessed on Mar. 3, 2021 at https://https://pubmed.ncbi.nlm.nih.gov/31317293/

18. "Demonstrating Biosimilarity Under the BPCI Act", Biosimilars Action Plan July 2018, U.S. Food & Drug Administration, last accessed on Dec. 20, 2020 at https://www.fda.gov/media/114574/download

19. Ibid, Nixon

20. "Biosimilar and Interchangeable Products—What is an interchangeable product? And What is the difference between a biosimilar and an interchangeable product?" web page, U.S. Food & Drug Administration web site, last accessed Dec. 15, 2020 at https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products

21. "Prescribing Biosimilar and Interchangeable Products: Can a Biosimilar or Interchangeable product be used in patients who have previously been treated with the reference product?" web page, U.S. Food & Drug Administration web site, last accessed Jan. 27, 2021 at https://www.fda.gov/drugs/biosimilars/prescribing-biosimilar-and-interchangeable-products

22."Biosimilar Development, Review, and Approval" web page, U.S. Food & Drug Administration web site, last accessed on Jan 27, 2020 at https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval Exhibit 2 Source: U.S. Food & Drug Administration, https://www.fda.gov/media/113355/download

23. James Smeeding, RPh, MBA, Daniel Malone, RPh, PhD, Monica Ramchandani, PhD, et al., "Biosimilars: Considerations for Payers", *Pharmacy and Therapeutics Journal*, Jan./Feb. 2019, Vol. 44 No. 2, Pages 54 - 63. Last accessed on Dec. 20, 2020 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6355057/pdf/ptj4402054.pdf

24. "Can a biosimilar be approved for an indication that is approved for the reference product even if the biosimilar is not directly studied in that indication?", Biosimilar Development, Review, and Approval: Oct. 20, 2017, U.S. Food & Drug Administration, last accessed on Feb. 5, 2021 at https://www.fda.gov/media/114574/download. https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval

25. "Schwartzberg Explains Biosimilar Use in Clinical Practice", The Center for Biosimilars page within the American Journal of Managed Care website, dated April 10, 2020, last accessed on Dec. 10, 2020 at https://www.centerforbiosimilars.com/view/schwartzberg-explains-biosimilar-use-in-clinical-practice

26. "FDA's Biosimilar Action Plan (BAP) Introduction and Overview: Balancing Innovation and Competition", Biosimilars Action Plan July 2018, U.S. Food & Drug Administration, last accessed on Dec. 20, 2020 at https://www.fda.gov/media/114574/download

27. "Key Elements of the BAP", Biosimilars Action Plan July 2018, U.S. Food & Drug Administration, last accessed on Dec. 20, 2020 at https://www.fda.gov/media/114574/download

28. "Biosimilar Product Information" web page, U.S. Food & Drug Administration web site, last accessed December 20, 2020 at https://www.fda.gov/drugs/biosimilars/biosimilar-product-information

29."Part B Biosimilar Biological Product Payment and Required Modifiers" web page, Center for Medicare & Medicaid Services web site, Page last modified: Feb. 20, 2018, last accessed Dec. 18, 2020 at https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/Part-B-Biosimilar-Biological-Product-Payment

30. Jackie Syrop, "CMS Reverses Its Policy on Biosimilar Reimbursement, Will Issue Unique J-Codes", The Center for Biosimilars, *American Journal of Managed Care* website, Published Nov. 3, 2017, last accessed on Dec. 20. 2020 at https://www.centerforbiosimilars.com/view/cms-reverses-its-policy-on-biosimilars-reimbursement-will-issue-unique-jcodes

31. "Medicare and Budget Sequestration—R45106", Congressional Research Service, Updated December 2, 2020, last accessed Dec. 18, 2020 at https://fas.org/sgp/crs/misc/R45106.pdf

32. "Medicare FFS Claims: 2 percent Payment Adjustment Suspended (Sequestration)", MLN Connects web page of the Centers for Medicare and Medicaid Services web site, Apr. 10, 2020, last accessed Dec. 18, 2020 at https://www.cms.gov/outreach-and-educationoutreachffsprovpartprogprovider-partnership-email-archive/2020-04-10-mlnc-se

33."Deemed to be a License" Provision of the BPCI Act web page, U.S. Food & Drug Administration web site, content current as of Apr. 4, 2020, last accessed on Dec. 30, 2020 at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/deemed-be-license-provision-bpci-act

34. "Mary Caffrey, "Diabetes Drugs Take Hits in Formulary Updates", American Journal of Managed Care, Aug. 3, 2016 published on-line, last accessed Dec. 18, 2020 at https://www.ajmc.com/view/diabetes-drugs-take-hits-in-formulary-updates

35. Ibid, Mulcahy

36. Surabhi Dangi-Garimella, PhD., "UnitedHealth's 2017 Formulary to Support Generic and Biosimilar Drugs", *American Journal of Managed Care*, published Sept. 23, 2016, last accessed Dec. 19, 2020 at https://www.ajmc.com/view/unitedhealths-2017-formulary-to-support-generic-and-biosimilar-drugs

37. "The U.S. Biosimilars market and Cigna affordability strategies", Cigna Pharmacy Management® CLINICAL UPDATE, published Dec. 2018, last accessed Dec. 20, 2020 at https://www.cignaproducer.com/pdf/Cigna_Biosimilars_Update_Flyer.pdf

38. Ibid, Mulcahy

39. Jayne Byrne, "Sandoz working to overcome barriers to greater biosimilars uptake in U.S.", BioPharma-Reporter.com, Published Sep. 21, 2020, last accessed on Dec. 20, 2020 at https://www.biopharma-reporter.com/Article/2020/09/21/Sandoz-working-to-overcome-barriers-to-greater-biosimilars-uptake-in-U.S.

40. Zachary Brennan, "U.S. Biosimilar Launches About to Turn a Corner", Regulatory Focus™ web page, Regulatory Affairs Professionals Society web site,

Posted Mar. 16, 2020, last accessed on Dec. 20, 2020 at https://www.raps.org/news-and-articles/news-articles/2019/12/us-biosimilar-launches-about-to-turn-a-corner

41. Scott Gottlieb, MD, Twitter Thread, posted Dec. 5, 2019, last accessed on Dec. 20, 2020 at https://twitter.com/ScottGottliebMD/status/1202723265539661825

42. Ibid, Mulcahy

43. Ibid, Mulcahy

44. "FDA Statement on efforts to help make development of biosimilar and interchangeable insulin products more efficient" web page, U.S. Food & Drug Administration web site, Content Current as of Nov. 27, 2019, last accessed on Jan. 27, 2021 at https://www.fda.gov/news-events/press-announcements/statement-efforts-help-make-development-biosimilar-and-interchangeable-insulin-products-more

45. Ibid, Smeeding

46. Luana Collaca, Remo Panaccione, and T. Kevin Murphy, "The Clinical Implications of Nocebo Effects for Biosimilar Therapy", *Frontiers in Pharmacology*, 2019; 10:1372, last accessed on Feb. 17, 2021 at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6895996/

47. "The nocebo response", Harvard Health Publishing, Harvard Medical School, Published March 2014, last accessed on Feb. 3, 2021 at https://www.health.harvard.edu/newsletter_article/The_nocebo_response

48. Liese Barbier, Hans C. Ebbers, Paul Declerck, et al., "The Efficacy, Safety and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review", First Published March 31, 2020, Clinical Pharmacology and Therapeutics, American Society for Clinical Pharmacology and Therapeutics, Oct. 2020, volume 108, Issue 4, P. 734-755, last accessed Dec. 30, 2020 at https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.1836

49. "Prescribing Biosimilar and Interchangeable Products: Can a Biosimilar or Interchangeable product be used in patients who have previously been treated with the reference product?" web page, U.S. Food & Drug Administration web site, last accessed Jan. 27, 2021 at https://www.fda.gov/drugs/biosimilars/prescribing-biosimilar-and-interchangeable-products#patients

50. Tyler Pernes, BA, Manthankumar Patel, MD, Nabeel Khan, MD, et al, "The Safety of Switching from Originator Infliximab or Biosimilar CT-P13 to SB2 Among a Nationwide Cohort of Inflammatory Bowel Disease Patients", Presented Poster P1597 (SO792), American College of Gastroenterology 2020 Annual Scientific Meeting, Oct. 26, 2020, last accessed Dec. 30, 2020 at https://www.eventscribe.net/2020/ACGPosters/PosterTitles.asp?PosterSortOrder=num&pfp=PosterNumber

51. B. Gleason, "Pharmacist Substitution of Biosimilars: An Overview of State Laws", M2 Health Care Consulting, published online May 30, 2016, last accessed on Dec. 20, 2020 at https://www.m2hcc.com/pharmacist-substitution-of-biosimilars-an-overview-of-state-laws.html

52. Richard Cauchi, "State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars", National Conference of State Legislatures, May 3, 2019, Last accessed on Jan. 27, 2021 at https://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx

53. Philip J. Schneider, MS, FASHP, "93 percent of Americans are Now Covered by Biosimilar Substitution Laws", Safe Biologics: Alliance for Safe Biologic Medicines web page, Published April 2018, last accessed on Dec. 20, 2020 at https://safebiologics.org/2018/04/93-of-americans-are-now-covered-by-biosimilar-substitution-laws/

54. B. Gleason, "Pharmacist Substitution of Biosimilars: An Overview of State Laws", M2 Health Care Consulting, published online May 30, 2016, last accessed on Dec. 20, 2020 at https://www.m2hcc.com/pharmacist-substitution-of-biosimilars-an-overview-of-state-laws.html

55. "Food and Drug Administration of First Biosimilar Product, MLN Matters® Number SE1509, Medical Learning Network, Centers for Medicare and Medicaid Services", last accessed on Dec. 30, 2020 at https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/SE1509.pdf

56. Peter Wehrwein, "Biosimilars for Cancer an "Emerging Success" Says NCCN's Koh", Managed Healthcare Executive, Published July 9, 2020, Managed Healthcare website, last accessed on Dec. 20, 2020 at https://www.managedhealthcareexecutive.com/view/biosimilars-for-cancer-an-emerging-success-says-nccn-s-koh

57. Chad Williamson, MBA, MS, Leanne Berger, BS, Thomas P. Sullivan, BS, et al., "Addressing Oncologists' Gaps in the Use of Biosimilar Products", Evidence-Based Oncology, June 2019,Volume 25, Issue 6, *American Journal of Managed Care* website, last accessed on Dec. 20, 2020 at https://www.ajmc.com/view/addressing-oncologists-gaps-in-the-use-of-biosimilar-products

58. Kelsey Waddill, "Payers Recommend Actions to Promote Biosimilars, Drug Competition", Policy and Regulation News web page, HealthPayer Intelligence etelligent Healthcare Media web site, Posted April 14, 2020, last accessed on Dec. 20, 2020 at https://healthpayerintelligence.com/news/payers-recommend-actions-to-promote-biosimilars-drug-competition

59. Ibid, Mulcahy

60. Ibid, Smeeding

61. Susan Morse, "Insurers cite cost as top factor in covering biosimilars", *Healthcare Finance* website, Published July 11, 2017, last accessed on Dec. 20, 2020 at https://www.healthcarefinancenews.com/news/insurers-are-covering-biosimilars-cost-top-factor

62. Rose Joachim, "Weighing the Potential of Humira Biosimilars in the U.S. - Competitive Dynamics Analysis", Biosimilar Development Guest Column - Sept. 29, 2020, last accessed Feb. 15, 2021 at https://www.biosimilardevelopment.com/doc/weighing-the-potential-of-humira-biosimilars-in-the-u-s-competitive-dynamics-analysis-0001

63. Ibid, Joachim

64. Ibid, Joachim

65. Ibid, Joachim

66. Ibid, Joachim

67. Hillel P Cohen, Dorothy McCabe, "The Importance of Countering Biosimilar Disparagement and Misinformation", *BioDrugs*, 2020 Aug; 34(4):407-414. Last accessed on Jan. 5, 2021 at https://pubmed.ncbi.nlm.nih.gov/32691270/

68. John Reddan, MBA, Jason Moore, MBA, Eric Snyder Ph.D., and Zi Yang, Ph.D, "Biosimilars: When Lower Cost Medications Mean Lower Provider Profits", *Navigant*, published 2017, Last accessed on Dec. 20, 2020 at https://guidehouse.com/-/media/www/site/insights/healthcare/2017/biosimilar-life-sciences-study.pdf

69. Tony Hagen, "CMS Payment Policy Plays Role in Biosimilar Uptake", Conference: Specialty Therapies and Biosimilars Conference, The Center for Biosimilars, American Journal of Managed Care website, Jan. 30, 2020, last accessed Jan. 5, 2021 at https://www.centerforbiosimilars.com/view/cms-payment-policy-plays-role-in-biosimilar-uptake

70. Jennifer Webster, Robert E. Smith, Danielle Wieland, et al., "Cost Savings of Biosimilar Pegfilgrastim in a Medicare OCM Population", *Journal of Clinical Oncology*, American Society of Clinical Oncology, DOI: 10.1200/JCO.2020.38.15_suppl.319362, published May 25, 2020, last accessed Dec. 20, 2020 at https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.e19362

71. Andrea Hassol, AbT Associates, "Evaluation of the Oncology Care Model: Performance Periods 1-3", contract #HHSM-500-2014-00261 T0003 for Center for Medicare and Medicaid Innovations, Centers for Medicare and Medicaid Services, Published May 2020, last accessed on Feb. 1, 2021 at https://innovation.cms.gov/data-and-reports/2020/ocm-evaluation-annual-report-2

72. Carol Lynch, "Biosimilars could disappear if the Supreme Court overturns the ACA", STAT First Opinion, published April 1, 2020, STAT web site, last accessed on Dec. 20, 2020 at https://www.statnews.com/2020/04/01/biosimilars-disappear-supreme-court-overturns-aca/

73. FDA. Biosimilar and Interchangeable Products. 2017. https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products

74. FDA. Capturing the Benefits of Competition for Patients. Speech by Scott Gottlieb, MD March 7, 2018. https://www.fda.gov/news-events/speeches-

fda-officials/capturing-benefits-competition-patients-03072018

75. Biosimilars Council. Biosimilars in the United States: Providing More Patients Greater Access to Lifesaving Medicines. 2019. https://biosimilarscouncil.org/wp-content/uploads/2020/04/Biosimilars-Patient-Access-Study.pdf

76. Winegarden, W. Promoting Biosimilar Competition to Reduce Patients' Out-of-Pocket Costs. Pacific Research Institute. March 2020. https://www.pacificresearch.org/wp-content/uploads/2020/03/BiosimilarReduceOutofPocket_Fweb.pdf

77. Winegarden, W. The Biosimilar Opportunity: A State Breakdown. Pacific Research Institute. 2019. https://www.pacificresearch.org/wp-content/uploads/2019/10/BiosimilarSavings_web.pdf

78. Ibid, Mulcahy

79. Ibid, Patel

80. "Biosimilar Basics for Patients", Patient Materials web page, U. S. Food and Drug Administration web site, content current as of 10/07.2020, last accessed Dec. 21, 2020 at https://www.fda.gov/drugs/biosimilars/patient-materials

81. Andrew D. Zelenetz, Islah Ahmed, Edward Louis Braud, et al., "NCCN Biosimilars White Paper: Regulatory, Scientific, and Patient Safety Perspectives", *Journal of the National Comprehensive Cancer Network,* Volume 9 Supplement 4, last accessed on Feb. 15, 2021 at https://jnccn.org/view/journals/jnccn/9/Suppl_4/article-pS-1.xml

82. Peter Wehrwein, "Biosimilars for Cancer an 'Emerging Success' Says NCCN's Koh", Managed Healthcare Executive, July 9, 2020, last accessed on Feb. 15, 2020 at https://www.managedhealthcareexecutive.com/view/biosimilars-for-cancer-an-emerging-success-says-nccn-s-koh

83. Gary Lyman, Edward Balaban, Michael Diaz, et al., "American Society of Clinical Oncology Statement: Biosimilars in Oncology", *Journal of Clinical Oncology*, 2018, Volume 36, Issue 12, last accessed on Feb. 15, 2021 at https://ascopubs.org/doi/10.1200/JCO.2017.77.4893

84. Sarah Nichelson, JD, "Update on Biosimilars", HOPA Biosimilars Issue Brief: Improving Access and Decreasing Costs for Cancer Patients, Hematology/Oncology Pharmacy Association HOPA News, Volume 16 Issue 3 (2019), last accessed on Feb. 15, 2021, at https://www.hoparx.org/images/hopa/advocacy/Issue-Briefs/biosimilars_brief_2019.pdf

85. Morgan B Frazer, Joseph Bubalo, Himanshu Patel, et al., "International Society of Oncology Pharmacy Practitioners global position on the use of biosimilars in cancer treatment and supportive care", *Journal of Oncology Pharmacy Practice,* Volume 26, Issue 3, supplement 2020, last accessed on Feb. 15, 2021 at https://journals.sagepub.com/doi/full/10.1177/1078155219893441

86. "The sluggish U.S. biosimilars market", from the Reports section of the Generics and Biosimilars Initiative (GaBi online) web site, Posted June 6, 2019, last accessed on Dec. 20, 2020 at http://gabionline.net/Reports/The-sluggish-US-biosimilars-market

87. How to support a viable U.S. Biosimilars market", from the Reports section of the Generics and Biosimilars Initiative (GaBi online) web site, Posted June 6, 2019, last accessed on Dec. 20, 2020 at http://gabionline.net/Reports/How-to-support-a-viable-U.S.-biosimilars-market

88. COA Biosimilars Position Statement, Community Oncology Alliance website, April 4, 2019, last accessed on Feb. 15, 2021, at https://communityoncology.org/biosimilars-community-oncology-alliance-position-statement/

89. Ibid, Smeeding

90. Andrew Donnelly, Jamie Paek, "Consider Adopting Biosimilars Into Clinical Practice", *Pharmacy Times,* Nov. 19, 2020, last accessed Feb. 16, 2021 at https://www.pharmacytimes.com/publications/health-system-edition/2020/November2020/consider-adopting-biosimilars-into-clinical-practice

91. Ibid, Smeeding

92. Ibid, Winegarden, The Biosimilar Opportunity: A State Breakdown

93. Ibid, Donnelly

94. Ibid, Donnelly

95. Skylar Jeremias, "Employers are in Good Position to Promote Biosimilars", The Center for Biosimilars, *American Journal of Managed Care,* April 7, 2020, last accessed on Feb. 16, 2021 at https://www.centerforbiosimilars.com/view/employers-are-in-good-position-to-promote-biosimilars

96. Ibid, Donnelly

97. Ibid, Smeeding

98. Ibid, Smeeding

99. Ibid, Mulcahy