



# BIOSIMILARS UPDATE: **2019 Report**

*Sixth Edition*

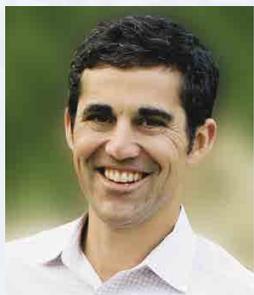


## Dear Colleagues,

The biosimilars landscape is rapidly evolving. As of early 2019, there are 7 biosimilar products that have launched in the United States (US), and many more are on the horizon. With this growth comes the continued need to reinforce with key stakeholders the potential benefits that biosimilars will bring to the US healthcare market.

We believe that the combination of our nearly 4 decades of experience in biologics development, manufacturing, and commercialization position Amgen as a leader and partner of choice in the biosimilars space. Amgen's commitment to reliably supply our biologics to every patient, every time, has resulted in zero shortages for more than a decade.

As an active participant in the ongoing national discussion, we are pleased to share with you the sixth edition of our Biosimilars Update. The 2019 report was developed based on input from various members of the US healthcare community and represents Amgen's continued commitment to being at the forefront of biosimilar education.



A handwritten signature in black ink that reads "Kave Niksefat".

Kave Niksefat  
Vice President  
US Value and Access, Amgen

# About Amgen

As one of the pioneers of modern biotechnology, Amgen's core focus is to discover, develop, and deliver innovative medicines. Now, nearly 4 decades later, Amgen is building upon our biotechnology heritage and expertise to develop and manufacture high-quality, reliably supplied biosimilars. We have made a significant commitment to biosimilars, with 10 products in development.

We are proud of being a dependable healthcare partner by supplying our biologics to every patient, every time. Ongoing data monitoring of drug shortages by the American Society of Health-System Pharmacists showed that Amgen was 1 of only 2 manufacturers with zero drug shortages from 2007 to 2017.<sup>1</sup>

At Amgen, we are also dedicated to providing industry-leading sales support and support services for patients, payers, pharmacists, and healthcare professionals. Our goal is to make the adoption of biosimilars as seamless and simple as possible.

We look forward to adding new chapters to our story, while maintaining Amgen's commitment to connecting patients with vital medicines.

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# Executive Summary

Since the first biosimilars entered the US marketplace in 2015, 17 products have been approved and 7 products have been launched.<sup>2</sup> The US marketplace is poised to welcome many new biosimilars in 2019 and 2020, spurring competition that will potentially lead to significant savings for the healthcare system.<sup>3,4</sup> Essential components of provider and patient use of biosimilars include addressing the clinical,<sup>5</sup> operational,<sup>6</sup> and economic<sup>7</sup> considerations to drive adoption as well as payer coverage.<sup>8,9</sup>

-  2019 and 2020 are expected to be pivotal years for biosimilars in the US, with multiple launches during this time frame.<sup>3,4</sup>
-  The availability of more biosimilars on the market will result in competition that has the potential to lead to significant savings for the healthcare system<sup>10</sup> and these savings can be deployed to newer, innovative treatments.
-  Current US regulatory standards for developing and approving biosimilars, as well as for establishing interchangeability, are scientifically appropriate to protect patient safety<sup>11</sup> and support provider<sup>12</sup> and payer<sup>13</sup> confidence. It is important to maintain these appropriate standards to support a sustainable biosimilars marketplace.
-  While financial savings are important for driving biosimilar uptake, they are not the only consideration for payers and providers. Other factors include manufacturer reputation for producing high-quality products, reliably supplying these products, and understanding provider and payer needs<sup>14,15</sup> and decision-making drivers.<sup>13</sup>
-  Trends show that providers are already aware of biosimilars and are interested in learning more about them.<sup>16,17</sup> Similarly, payers are showing a desire to adopt biosimilars to foster a successful marketplace and realize savings.<sup>7</sup> Also, biosimilar adoption is not the only measure of success. Reference products may lower prices to compete and to attempt to retain market share.<sup>18</sup> This is also a positive outcome that results from biosimilar competition.
-  Many competitive mechanisms already exist to support biosimilar uptake. The Centers for Medicare and Medicaid Services (CMS) have made important changes to the current US reimbursement system, such as establishing separate Healthcare Common Procedure Coding System (HCPCS) codes and payment rates for biosimilars to support their uptake, which can help lead to meaningful cost savings and a sustainable marketplace.<sup>19</sup>



# CURRENT STATE OF THE MARKET

# Current State of the Market

As of January 2019, the US Food and Drug Administration (FDA) had approved 17 biosimilars, as shown in **Table 1**. With 7 products launched in 4 therapeutic areas,<sup>2</sup> these are still the early days of the biosimilar marketplace in the US, and the next 2 years (2019–2020) will likely see more biosimilar launches. The FDA created a program to provide detailed, product-specific advice to manufacturers that plan to submit applications for biosimilar approval. The number of manufacturer biosimilar programs enrolled in the FDA’s biosimilar development program was 68 as of July 2018, with the number of programs enrolled expected to exceed 90 in 2019.<sup>3,4</sup>

As evidenced from the adoption of biosimilars in Europe over the last 12 years, manufacturers, payers, and providers in the US expect biosimilar competition will potentially lead to consistent price reduction.<sup>20</sup> These savings can be invested in spending for new, innovative medicines and can reduce patient out-of-pocket costs.

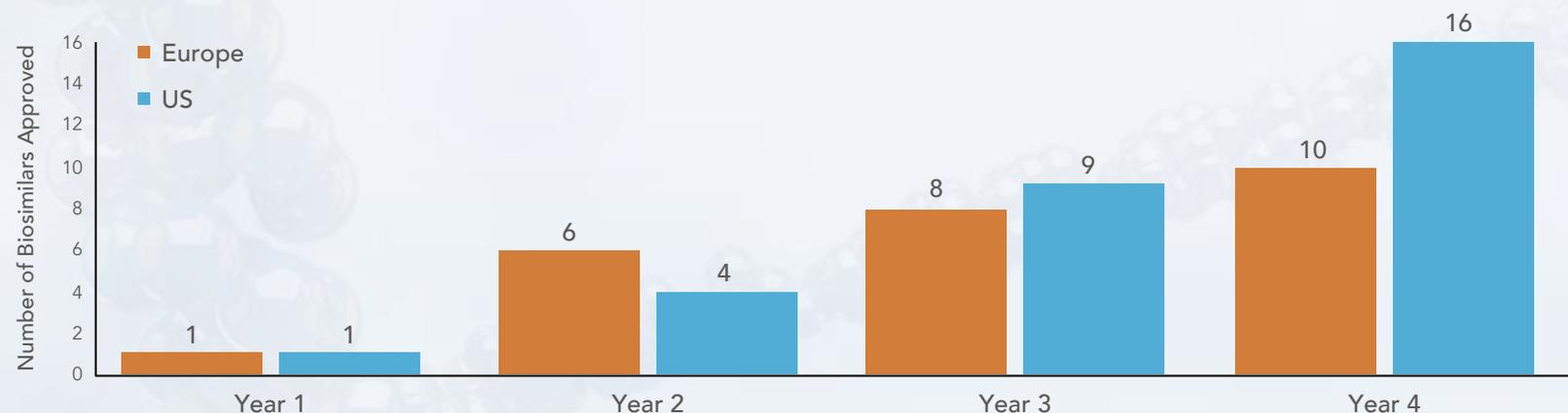
It only takes 1 to 2 biosimilars on the market to result in meaningful cost savings to the healthcare system.<sup>21</sup>

## Comparison of Biosimilar Markets in Europe and the US

Europe has an advanced biosimilar market, with more approved products than the US (53 vs 17).<sup>22,23</sup> However, it should be noted that the 53 approved biosimilars in Europe are not distinct compounds. Some of the approved biosimilars are different brand names marketed under duplicate marketing authorizations or the same application. When the 2 markets are compared, starting from the point when they approved their first biosimilar, the US shows a higher rate of approvals. As **Figure 1** shows, by the end of Year 4, Europe had 10 biosimilars approved and the US had 16.<sup>22,23</sup>

**Figure 1. Comparison of Europe and US Biosimilar Markets<sup>22,23</sup>**

Cumulative Number of Biosimilars Approved for Marketing in Europe vs the US, Beginning With Year the First Biosimilar Was Approved



**Table 1. Biosimilars in Development and Approved by the FDA in Hematology, Inflammation and Immunology, and Oncology Therapeutic Areas\***

Manufacturer	Number of Biosimilars in Preclinical, Phase 1, Phase 2, Phase 3, or Submitted to FDA†	Number of Biosimilars Approved by the FDA	Relevant Therapeutic Areas
<b>Adello Biologics</b> <sup>‡,24</sup>	3		Hematology, Immunology & Inflammation
<b>Amgen</b> <sup>25,26</sup>	5	2	Inflammation & Immunology, Oncology
<b>Apobiologix (Apotex)</b> <sup>27</sup>	7		Hematology, Inflammation & Immunology, Oncology
<b>Archigen (Samsung BioLogics/AstraZeneca)</b> <sup>28</sup>	1		Inflammation & Immunology, Oncology
<b>Boehringer Ingelheim</b> <sup>29</sup>	1	1	Inflammation & Immunology, Oncology
<b>Celltrion</b> <sup>30,31</sup>	5		Inflammation & Immunology, Oncology
<b>Celltrion/Teva</b> <sup>30-32</sup>		2	Inflammation & Immunology, Oncology
<b>Coherus BioSciences</b> <sup>33</sup>	2	1	Hematology, Inflammation & Immunology
<b>Formycon/Aristo Pharma GmbH</b> <sup>34</sup>	1		Inflammation & Immunology
<b>Fresenius Kabi</b> <sup>35,36</sup>	2		Hematology, Inflammation & Immunology
<b>mAbxience</b> <sup>37</sup>	2		Inflammation & Immunology, Oncology
<b>Mylan/Biocon</b> <sup>38</sup>	4	2	Hematology, Inflammation & Immunology, Oncology
<b>Mylan/Mabion</b> <sup>38</sup>	4		Inflammation & Immunology, Oncology
<b>NeuClone</b> <sup>39</sup>	5		Inflammation & Immunology, Oncology
<b>PfEnex</b> <sup>40</sup>	2		Hematology
<b>Pfizer</b> <sup>41-44</sup>	4	5	Hematology, Inflammation & Immunology, Oncology
<b>Prestige BioPharma</b> <sup>45</sup>	5		Inflammation & Immunology, Oncology
<b>Samsung Bioepis/Merck</b> <sup>46</sup>	3	2	Inflammation & Immunology, Oncology, Rare Disease
<b>Sandoz</b> <sup>47</sup>		3	Hematology, Inflammation & Immunology
<b>Xbrane Biopharma</b> <sup>48</sup>	2		Hematology, Inflammation & Immunology
<b>TOTAL</b>	<b>58</b>	<b>18</b>	

\* The table lists biosimilars for selected therapeutic areas and may not be all-inclusive.

† Totals based on publicly available information. Additional biosimilars could be in preclinical or phase 1 development and not yet reported publicly.

‡ Acquired by Kashiv Pharma on January 3, 2019.<sup>49</sup>

Key: FDA – Food and Drug Administration.

At this point, the rate of regulatory approvals in the US is slightly ahead of Europe during a comparable time period and is expected to accelerate, as many biosimilars are currently in advanced stages of development.<sup>22,23</sup>

A lesson learned from the European biosimilar market is that there are many factors that are considered in selecting a biosimilar product, such as:



Manufacturer heritage and expertise in developing, manufacturing, and reliably supplying biological medicines, including logistics, inventory management, and environmental impacts of production



Support programs for patients



Provider education

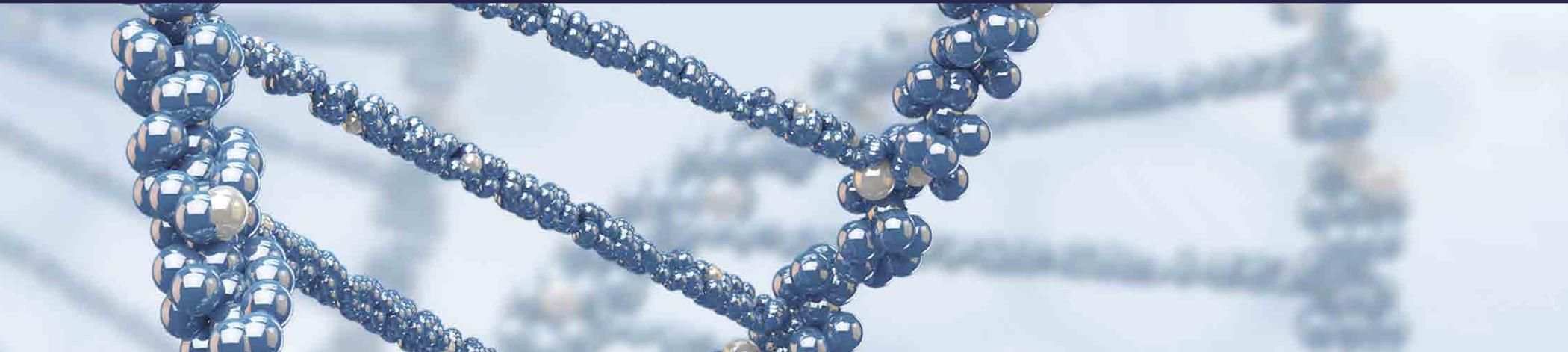


Product attributes, such as packaging, storage, stability, excipients, dosage forms and strengths; routes of administration; and device designs



Available pre-clinical and clinical data, real-world evidence generation

Also, biosimilar adoption is not the only measure of success. Reference products may lower prices to compete and to attempt to retain market share.<sup>18</sup> This is also a positive outcome that results from biosimilar competition.

A close-up photograph of a blue beaded necklace, showing several strands of small, round, metallic-looking blue beads. The necklace is draped and slightly out of focus in the background, creating a sense of depth. The lighting highlights the texture and color of the beads.

# BIOSIMILARS OVERVIEW

# Biosimilars Overview

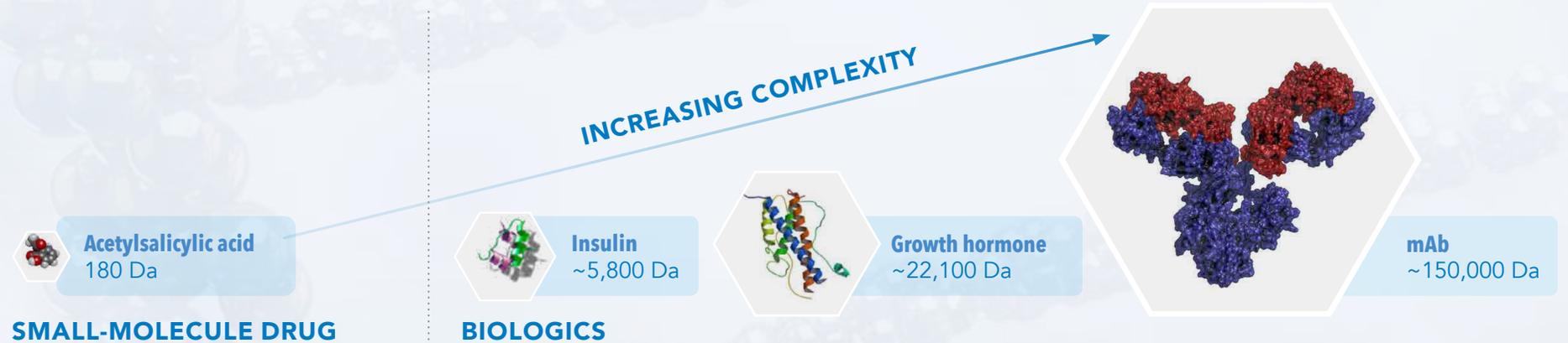
## Understanding Biosimilars

A biosimilar is a biologic that is clinically similar in its safety and efficacy to, and is approved based on a comparison to, an approved originator (or reference) product.<sup>50</sup>

There are fundamental differences in the complexity and development of biosimilars and complex biologics compared to small-molecule generic and branded drugs.

- Biosimilars are not “generics”—they are biologics that are highly similar to, and have no clinically meaningful differences from, the FDA-approved reference products.<sup>51</sup>
- By contrast, generics are drugs that are chemically and therapeutically equivalent to the branded, originator small-molecule drugs.<sup>52</sup>
- Compared to small-molecule drugs, including generic medicines, biosimilars are large-molecule drugs that are **far more structurally complex**.<sup>53</sup>
- The pathway for FDA approval of biosimilars was specifically established by Congress **not** to mirror the generic drug route.

**Figure 2. Comparison of Size and Complexity of Small-Molecule Drugs and Biologics<sup>54-58</sup>**



GENERICS: Same structure as reference drug

BIOSIMILARS: Highly similar structure to reference biologic

Key: Da – dalton, 1 atomic mass unit; mAb – monoclonal antibody.

## US FDA Approval Pathway for Biosimilars

The Biologics Price Competition and Innovation Act (BPCIA), signed into law as part of the Affordable Care Act (ACA) in 2010, established the abbreviated approval pathway for biosimilars in the US.

Because biologics contain active substances derived from living cells or organisms, the development of a biosimilar is much more complex than the process for developing a generic drug. A biosimilar requires the creation of a new manufacturing process and a custom cell line, since the reference product's manufacturing process is proprietary and not publicly available.<sup>59</sup>

Due to the complex nature and production methods of biologics, relatively minor changes in manufacturing processes may significantly affect product quality, safety, and the criteria by which similarity is determined.<sup>60,61</sup> Because of this, providers, payers, and patients may consider a manufacturer's reputation for quality and reliable supply as a key factor when making decisions.

Based on the provisions in the BPCIA, the FDA recommends a step-by-step biosimilar development approach. At each step in development, an applicant should do the following:

- Identify any differences between the reference and biosimilar products
- Determine what residual uncertainty remains based on the potential impact of the observed difference
- Design subsequent studies to address the remaining residual uncertainty<sup>5,60</sup>

As shown in **Figure 3**, while a biosimilar may require more analytical characterization and nonclinical studies than reference products, it may need fewer clinical trials and clinical pharmacology studies than its reference product to obtain FDA approval.<sup>5</sup> Due to this reliance on the FDA's previous finding of safety and effectiveness for the reference product, a biosimilar may have a shorter and less costly development program.

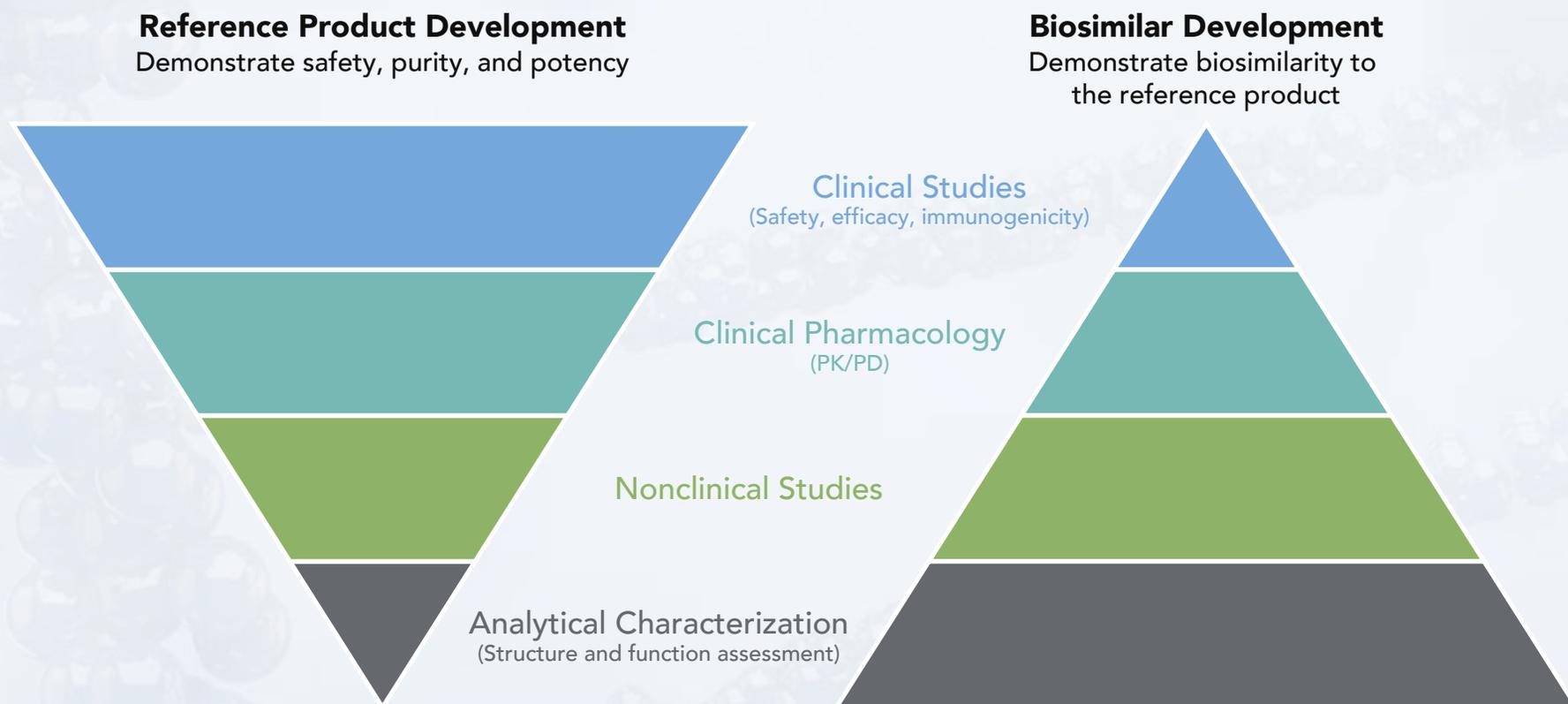
The BPCIA's abbreviated licensure pathway allows for reliance on the FDA's previous finding of safety and effectiveness for the reference product, promoting a potentially shorter and less costly development program for biosimilars.<sup>5</sup>

The goal of a biosimilar development program is not to re-establish the safety and efficacy of the reference product, but to demonstrate that the proposed biologic product is biosimilar to the reference product.<sup>5,60</sup> No single study is considered "pivotal" to a biosimilar application; rather, the totality of data and information submitted to the FDA support the demonstration of biosimilarity.<sup>5</sup>

When administered to patients, all biologics—including biosimilars—have the potential to induce an unwanted immune response (ie, to stimulate the formation of antidrug antibodies). The impact of immune responses, or “immunogenicity,” can range from no apparent effect to changes in pharmacokinetics, loss of effect, and serious adverse events.<sup>62</sup>

Understanding a biologic’s immunogenicity profile is key to establishing the safety profile of all biologics. A head-to-head assessment comparing immunogenicity of the biosimilar with that of the reference product is, therefore, of critical importance. It is considered a key component of a biosimilar’s clinical development program.<sup>62</sup>

**Figure 3. Reference Product Development vs Biosimilar Development<sup>5</sup>**



Key: PK/PD – pharmacokinetics/pharmacodynamics.

## Extrapolation

While reference products with multiple indications require clinical studies to establish safety and efficacy for each indication, biosimilars are not required to be evaluated clinically in every indication held by the reference product; instead, the FDA may consider “extrapolating” clinical efficacy and safety data from one indication to support the approval of a biosimilar for another indication. In fact, the FDA has said that extrapolation is critical to providing options at a potentially lower cost.<sup>63</sup>

The expectation for most biosimilar drugs is that they will be approved for the same indications as the reference product.

Labeling may be identical to the reference drug across several indications, but the biosimilar may be approved with fewer indications than the reference product due to a manufacturer’s inability to provide adequate scientific justification for extrapolation or to intellectual property protections.<sup>64,65</sup>

The biosimilar manufacturer must provide scientific justification to support extrapolation, which may include knowledge of the mechanisms of action, pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity of the reference product.<sup>60</sup>

## Determination of Interchangeability, Switching, and Substitution

A “biosimilarity” determination allows market entry but not pharmacy substitution. Per US state pharmacy laws (45 states have passed legislation, including Puerto Rico), a biosimilar may not be substituted at the pharmacy unless the FDA has designated it as “interchangeable” with its reference product.<sup>66</sup> The FDA grants a biosimilar “interchangeable” status if the manufacturer demonstrates:

The product can be expected to produce the same clinical result as the reference product in any given patient

For a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and the reference product is not greater than the risk of using the reference product without such alternation or switch<sup>67</sup>

Unlike small-molecule generic drugs, biosimilars are not identical to their reference products, and therefore are not substitutable at the pharmacy without an “interchangeable” designation. An interchangeable biosimilar product, on the other hand, may be substituted for the reference product by a pharmacist without the involvement of the prescriber (pursuant to state pharmacy laws)—much like how generic drugs that have been deemed “therapeutically equivalent” can be substituted for their brand drugs by a pharmacist.

So far, the FDA has not designated any biosimilar to be interchangeable to its reference product.<sup>68</sup> As of January 2019, only 1 manufacturer had publicly announced an effort to seek interchangeability status.<sup>69,70</sup>

A January 2018 report that gathered information from 10 medical directors at 10 US payer organizations, which represented plans covering 100 million commercial and Medicare lives, found that an interchangeability designation would make it easier for payers and pharmacies to encourage switching and even implement automatic substitution.<sup>71</sup>

The FDA has issued draft guidance describing its expectations of manufacturers for demonstrating interchangeability. For biologics administered more than once to a patient, the draft guidance recommends a “dedicated switching study” design, in which patients start with the reference product and are randomly assigned to switch to the biosimilar or to continue using the reference product.<sup>67</sup> The “switching” patient group would be expected to incorporate at least 3 switches between the reference and biosimilar product.

In the absence of the FDA or a state permitting the automatic substitution of biosimilars, hospitals, health plans, and pharmacy benefit managers (PBMs) may consider the use of a formulary-management technique called “therapeutic interchange” as the mechanism to effectively substitute a biosimilar for its reference product. Therapeutic interchange is the process of reimbursing one product rather than another when both products are expected to produce similar clinical effects and outcomes based on scientific evidence. Many health systems today use therapeutic interchange for a variety of drugs and biologics to lower costs.<sup>72</sup>

### Manufacturer Reliability

It will be essential for biosimilar supplies to be reliable in order for these products to succeed.<sup>73</sup> Manufacturers may experience periods of reduced supply of biologics, including biosimilars, during times of high demand, particularly for oncology drugs.<sup>74</sup>

#### Potential effects of drug shortages may include:<sup>75</sup>

Drug rationing and need to prioritize patients

Increased costs across the system

Time burden involved in managing shortages

Compromised patient care

Errors due to inexperience with alternatives

A manufacturer of a proposed interchangeable product must show the product is biosimilar to a reference product and that it can be expected to produce the same clinical result as the reference product in any given patient.<sup>67</sup>

*Biosimilars have a bright future if additional work is done to be attractive to prescribers and payers. I still expect they will get 50% [market share] but only if there is steep discounting or interchangeability status.<sup>71</sup>*

- Medical director, large national payer

Given potential immunogenicity concerns, including the technical challenges in developing and producing a biosimilar that matches all the key characteristics of the reference product, an important consideration is the manufacturer's experience, record of consistent manufacturing, proven capacity, and stable supply chain.<sup>76</sup>

Manufacturer reliability can play a large role when payers are reviewing these products for formulary consideration.<sup>73</sup> Providers and payers will likely seek or create policies to use a consistent biosimilar from a reliable manufacturer to reduce the need for switching from one product to another because of supply limitations or disruptions.

## Pharmacovigilance and Naming

Pharmacovigilance, the monitoring and tracking of drug safety over time, is important to detect any emerging safety signals.<sup>77</sup> To help facilitate pharmacovigilance, the FDA released final guidance on the nonproprietary naming of biological products (including biosimilars) in January 2017.<sup>78</sup>

Generic drugs and brand drugs share the same nonproprietary name because they are chemically identical.<sup>79</sup> However, reference biologics and biosimilars are highly similar but not chemically or biologically identical. Distinguishable nonproprietary names facilitate pharmacovigilance and help avoid inappropriate substitution at the pharmacy level.<sup>78</sup>

Under the guidance, each originator biologic, related biologic, and biosimilar will be assigned a nonproprietary name consisting of a core name and a hyphenated distinguishing suffix of 4 lowercase letters.<sup>78</sup>

The example in **Table 2** shows the illustrative hypothetical nonproprietary names of a reference product and its biosimilar:

**Table 2. Comparison of Nonproprietary Names of Reference Products and Biosimilars<sup>78</sup>**

	Core Name	Distinguishing Suffix
Reference Product	Same Core Name	-abcd
Biosimilar	Same Core Name	-efgh

One of the FDA's goals, as stated in the final guidance on naming, is to use distinguishable suffixes to facilitate pharmacovigilance and to prevent inadvertent substitution.<sup>78</sup>

The guidance will also help promote proper attribution of safety events and effective tracking of biosimilars.<sup>78</sup> The benefits of the naming convention should bolster patient and physician confidence, and encourage manufacturer accountability by providing additional ways to ensure that prescribed products may be tracked appropriately.<sup>78</sup> Additionally, when interchangeable products enter the US market, the unique suffixes will help to minimize risk that a noninterchangeable product is substituted in place of the prescribed reference product.

Distinct nonproprietary names can help avoid inappropriate substitution, promote proper attribution of safety events, and facilitate effective tracking and tracing of biologics.



# BENEFITS AND CONSIDERATIONS

# Benefits and Considerations

Biosimilars offer potential benefits to every stakeholder in the healthcare system. They can lower spending by offering a potentially lower-cost treatment option and can help improve patient outcomes by providing additional treatment options. Also, competition fostered by the introduction of biosimilars can lead to savings that can be redeployed toward spending on new, innovative therapies.

Compared to the reference products, biosimilars may create opportunities to lower spending for payers, employers, state and federal governments, and patients.<sup>80</sup> Two factors can primarily drive these savings:

## Developing a biosimilar costs less than a reference biologic because of the abbreviated FDA approval pathway

Biosimilars are expected to take 8 to 10 years to develop, at a cost between \$100 million and \$200 million compared to an estimate of \$2.6 billion for developing a new drug or biologic.<sup>59,81</sup> As a result, manufacturers have fewer expenses to recoup, which theoretically allows for biosimilars to have lower list prices.

## Biosimilars contribute to competition in the healthcare system

As the number of treatment choices increases for a particular disease or condition, manufacturers may be incentivized to lower the prices of their products to maintain or increase market share.



*Biosimilars will create long-term cost savings and efficiencies, free up resources for other important aspects of cancer care. In doing so, biosimilars could expand cost-effective care to millions more patients—a much-needed step in reducing spending.<sup>82</sup>*

- U.S. News & World Report,  
April 24, 2018

## Meaningful Savings From Marketplace Competition

Based on the initial experience with biosimilars, market competition may create savings for patients and the healthcare system. The first 2 biosimilars on the US market (for different reference products) had wholesale acquisition costs (WACs) 15% below their reference products, with the WAC for one of them subsequently decreasing to 20% below the reference biologic.<sup>42,83</sup> In addition to biosimilar manufacturers facing pressure to discount to compete, manufacturers of reference products may also discount their products; this price competition increases savings.

A level playing field for reimbursement helps the introduction of competition from biosimilars to generate downward pressure on reference product prices—leading to potentially even greater spending reductions.<sup>84</sup>



The RAND Corporation, a nonprofit, nonpartisan research organization, estimated in 2014 that biosimilars would reduce direct spending on biological drugs by \$54 billion from 2017 to 2026, or about 3% of total estimated biological spending over the same period, with a range of \$24 billion to \$150 billion.<sup>80</sup>

Strong competition on a level playing field is the best way to achieve a sustainable biosimilar market with meaningful cost savings for the healthcare system in a way that builds stability and can be realized over the long term. A typical consequence of a strong, competitive marketplace is that prices for goods or services decrease as more competitors enter the market.<sup>85</sup> An ongoing commitment to driving competition will help create a sustainable US biosimilar market. A 2016 report from IMS Health noted that biosimilars enable stakeholders—including payers, physicians, and patients—to benefit from increased choice in therapeutic options.<sup>21</sup>

Competition lies at the center of the biosimilar value proposition, driving pharmaceutical innovation and affirming healthcare system sustainability.

## Considerations

### **Need for Appropriate Scientific Standards**

The scientific and regulatory framework currently in place in the US is sufficient to ensure that approved biosimilars are safe and effective. The FDA applies similar manufacturing standards for all biological products, and there is one good manufacturing practice (GMP) standard for all biological products, including biosimilars.<sup>86</sup> To promote patient safety, manufacturing standards should be the same regardless of whether the biologic is a reference product or a biosimilar.

### **The Importance of Confirmatory Clinical Studies**

Biosimilars require fewer clinical trials for FDA approval than reference products.<sup>87</sup> That shorter time frame is by design.

The focus for the manufacturer of a reference biologic is to clearly demonstrate safety and efficacy of the therapeutic in multiple, lengthy clinical trials.<sup>88</sup> The biosimilar approval pathway is more targeted in that it requires fewer clinical studies compared with the reference biological product. However, the testing of a biosimilar includes a greater emphasis on analytical studies in order to demonstrate similarity with the biological reference product.<sup>87</sup>

It is important to study biosimilars in clinical studies and sensitive patient populations to establish clinical equivalence and to assess immunogenicity risk. This builds patient and physician confidence.

Since the US biosimilar market is still in the early stages, continued science-based education about these medicines will provide stakeholders with greater confidence in their use. The FDA and those manufacturers and organizations committed to scientifically accurate education are well positioned to inform physicians, patients, payers, and the groups that represent them about biosimilars.

The BPCIA created an abbreviated, yet rigorous, regulatory approval pathway for biosimilars as a mechanism to promote innovation and competition in the development of biologics and to open an avenue to lower their cost.<sup>87</sup>

### Influential stakeholders

Physicians and payers play an important role in biosimilar acceptance and usage, and patients need assurance that biosimilars are as safe and effective as reference biologics. Since biosimilars are a new class of products, there may be concerns that these stakeholders are not familiar or comfortable enough to use biosimilars.<sup>89</sup>

### Gaining support for and confidence in biosimilars

Requires stakeholders understanding that biosimilar approval is supported by evidence demonstrating that the biosimilar provides similar efficacy and safety as the reference product.<sup>90</sup> As the market matures, the comfort level with biosimilars should increase as physicians and payers are becoming more informed about biosimilars and more comfortable with prescribing them or adding them to formularies.



# KEY STAKEHOLDER: **Healthcare Professionals**

# Key Stakeholder: Healthcare Professionals

Healthcare professionals, including physicians, physician assistants, nurse practitioners, and pharmacists, are an extremely important group that can help educate patients and increase the adoption of biosimilars. Physicians must have the confidence to prescribe biosimilars, and all healthcare professionals must have confidence in the evidence and the approval process supporting their licensure.

In addition to educating their patients, providers should also ensure that their practices have operational processes in place to prepare for using biosimilars. Also, practices and institutions such as hospitals will need confidence that biosimilars are covered by payers and are reimbursed in a timely fashion.

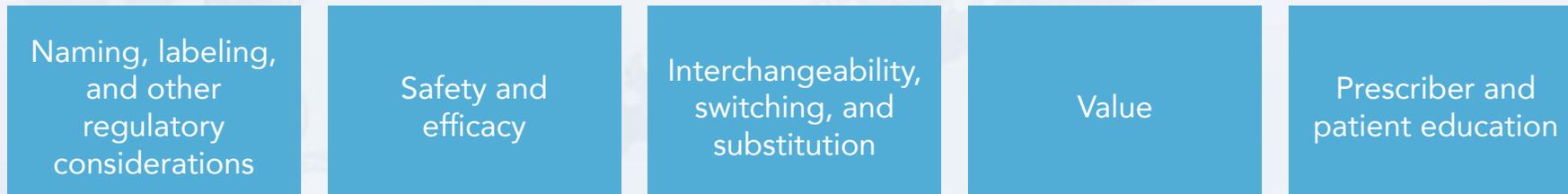
## Biosimilar Education

The concept of biosimilars is relatively new, so science-based education about these products will provide stakeholders with greater confidence in their use. One area to be emphasized is that although biosimilars are not exactly the same as the reference product, they are highly similar and have been demonstrated to have no clinically meaningful differences in terms of safety, efficacy, purity, or potency from the reference products.<sup>5,60</sup>

Educational campaigns by the FDA and organizations such as the Biologics Prescribers Collaborative, American Society of Clinical Oncology (ASCO), Pharmaceutical Research and Manufacturers of America, and Biotechnology Innovation Organization include scientific information about how biosimilars are manufactured and developed, how they are approved by regulators, the concept of extrapolation, and clinical considerations for use. Five years after the FDA approved the first biosimilar in the US, physicians and other healthcare providers are generally knowledgeable about them, with most being open to receiving additional education.<sup>91,92</sup>

Specialty societies of physicians, nurse practitioners, and others are recognizing the promise of biosimilars for providers and patients, so these groups have been placing increasing importance over the last few years in educating their members about biosimilars.<sup>93,94</sup> In 2018, ASCO published a policy statement in its clinical journal and on its website to help bridge the gap of understanding biosimilars among the cancer care community.<sup>95</sup>

Their guidance focuses on:<sup>95</sup>



While the education gap is narrowing, some healthcare providers continue to be wary of prescribing biosimilars in place of reference products. A 2018 survey of 442 clinicians, conducted by the Health Research Institute of PricewaterhouseCoopers, found that 55% of clinicians were unfamiliar with biosimilars, with 35% saying they have never prescribed them.<sup>96</sup> Sixty-five percent of respondents indicated they would be more willing to prescribe biosimilars if there was a meaningful cost difference for their patients.<sup>96</sup>

Not all specialties show this reticence toward biosimilar prescribing, with the most recent surveys showing that specialists who are heavy users of biologics (eg, oncologists and hematologists) have knowledge about biosimilars and are confident about prescribing them to their patients.<sup>91,92</sup>

In results published in 2018, as described in **Table 3**, 510 US-based community oncologists, hematologists, and practice administrators were asked about their familiarity with biosimilars. Their responses showed a high comfort level with the products.<sup>91</sup>

**Table 3. US Community Oncologists' and Hematologists' Familiarity With Biosimilars<sup>91</sup>**

Response to Survey Questions*	% of Respondents (Physicians)
<b>Very or somewhat familiar with biosimilars (n=302)</b>	79
<b>Aware of the currently approved biosimilars with oncologic indications (n=63)</b>	92
<b>Prescribed a biosimilar at some point in the preceding 12 months (n=196)</b>	65
<b>Very or somewhat confident that biosimilars are as safe and effective as reference biologics (n=40)</b>	95

\* Not all questions were asked in each of the meetings, and not every respondent answered all questions; therefore, there was a variability in the number of respondents for each question.

## Operational Processes

Savings expected from biosimilars are particularly important when considering that hospital systems and provider groups are focused on cost savings while providing quality care.

Health systems and providers will need to prepare for the growing availability of biosimilars by:



Anticipating differences in delivery device between a reference product and a biosimilar



Understanding how to differentiate electronic health records when stocking the reference product and biosimilar<sup>97</sup>



Being familiar with major payers' coverage and reimbursement policies for biosimilars

## High-Quality, Reliable Supply

The FDA holds all biologics—both reference products and biosimilars—to the same GMP standard during the approval process.<sup>98</sup> Biosimilar manufacturers must have a long-term commitment to quality for the biosimilars market to succeed.

Providers should consider a manufacturer's history of shortages and recalls related to quality concerns, and evaluate its capability to maintain adequate production and stock to support demand when deciding to use any product. Providers and patients should also consider the robustness of the manufacturer's supply chain when evaluating product use.<sup>54</sup>

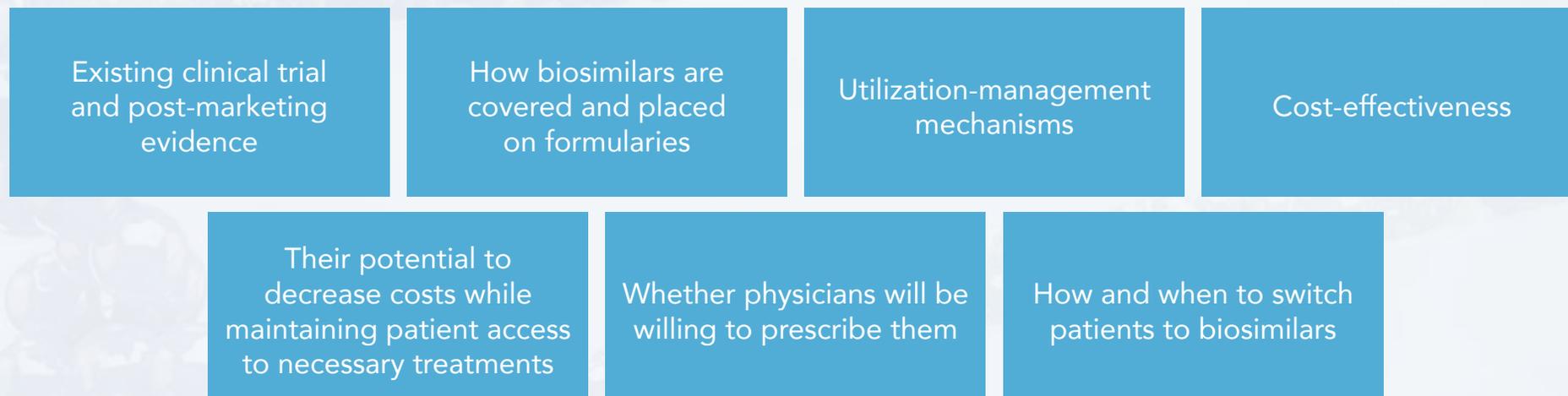


# KEY STAKEHOLDER: **Payers and Employers**

# Key Stakeholder: Payers and Employers

## Payers

Payers are looking to biosimilars as an opportunity to better control costs and offer more treatment choices.<sup>7</sup> For biosimilars, payers must evaluate a number of clinical and economic considerations, including:



Increasingly, payers are showing a desire to embrace biosimilars, which could help lower costs for the US healthcare system.

Depending on the therapeutic class, payers may determine that it is in the best interest of patients to maintain access for the reference product and biosimilars. This may be most relevant for drugs such as oncology therapeutic drugs or drugs that treat chronic conditions where patients are stable on therapy.

Similar to providers, payers should have confidence in the safety and efficacy of biosimilars, because the BPCIA defines a biosimilar as a biological product that is highly similar to, and has no clinically meaningful differences from, an existing FDA-approved reference product.<sup>99</sup> The current regulatory environment supports the uptake of biosimilar products by payers, providers, and patients because all biological products must be held to the same quality standards, including reference products and biosimilars.

Uptake of biosimilars is not the only metric of success. Reference products may also have to lower prices to compete, which may result in savings but may also result in reference products maintaining significant market share.

Biosimilars offer the promise of cost savings for payers for both the reference product and the biosimilar. Manufacturers of reference products may have incentive to offer price concessions to compete and maintain formulary access. Biosimilar manufacturers may offer lower prices relative to the reference product in exchange for formulary access as well.

Some large payers and PBMs are preferentially covering FDA-approved biosimilars, while others are covering both reference and biosimilars, but the reference product requires prior authorization.<sup>100-103</sup>

## Employers

Employers are a prime audience for biosimilars because 156.2 million people (49% of the US population) have employer-sponsored insurance—more than any other payer type.<sup>104</sup> As a result, employers command great influence in the healthcare system. Employers also have a vested interest in controlling and containing healthcare costs, not only for themselves but also for their employees, who are absorbing a greater percentage of healthcare costs each year.

Escalating healthcare costs, historically low interest rates, and an aging workforce have made employee benefits a significant line item for employers over the last 10 years. The cost of providing employee benefits in the US increased 24% between 2001 and 2015, fueled largely by a doubling in healthcare benefit costs.<sup>105</sup>

**Biosimilars work best in a competitive environment, with a level playing field for reimbursement. Payers are excited about the wave of biosimilars coming to the market, as they understand the positive results for patients, providers, and the entire healthcare system. Their confidence in biosimilars is evidenced by a number of plans and PBMs replacing reference products with biosimilars on their formularies or designating the biosimilars as preferred products.**

Although insurers' medical cost trends (ie, cost increases for medical products or services, combined with utilization of products and services) have moderated in recent years, they still ranged between 5.5% and 9% per year since 2011.<sup>106</sup>

Escalating specialty drug costs present a challenge for many employers trying to afford their healthcare spend while maintaining a profitable business. Greater biosimilar market penetration could help to increase competition and lower costs without compromising quality, efficacy, or patient safety.

A 2018 study by the Pacific Research Institute found that if biosimilars can reach 50% of the market for a popular biologic, the annual cost reductions for employer-sponsored health plans could be as high as 8.4%, or between \$262 million and \$315 million in annual cost savings, depending on the actual average mark-up percentage.<sup>107</sup>

The National Alliance of Healthcare Purchaser Coalitions provided steps for employers to “influence change that will ultimately lead to more options for employees and their dependents who are dealing with diseases like cancer, rheumatoid arthritis, inflammatory bowel disease, diabetes, multiple sclerosis, kidney disease, and severe psoriasis”:<sup>108</sup>



Quantify the biosimilar opportunity by initiating conversations with vendors about fill rates and savings potential



Partner with vendors to determine how best to drive appropriate promotion, adoption, and utilization of biosimilars



Review specialty pharmacy benefit design to ensure that it supports appropriate use and access



Educate all employees about the value of biosimilars to enable more informed decision making



# REIMBURSEMENT

# Reimbursement

Marketplace competition through a level playing field for reimbursement is critical for a viable and competitive biosimilar market. The market share of biosimilars compared to reference products is not the only measure of success—competition that leads to savings is most important, whether providers and payers continue to choose reference products or biosimilars.

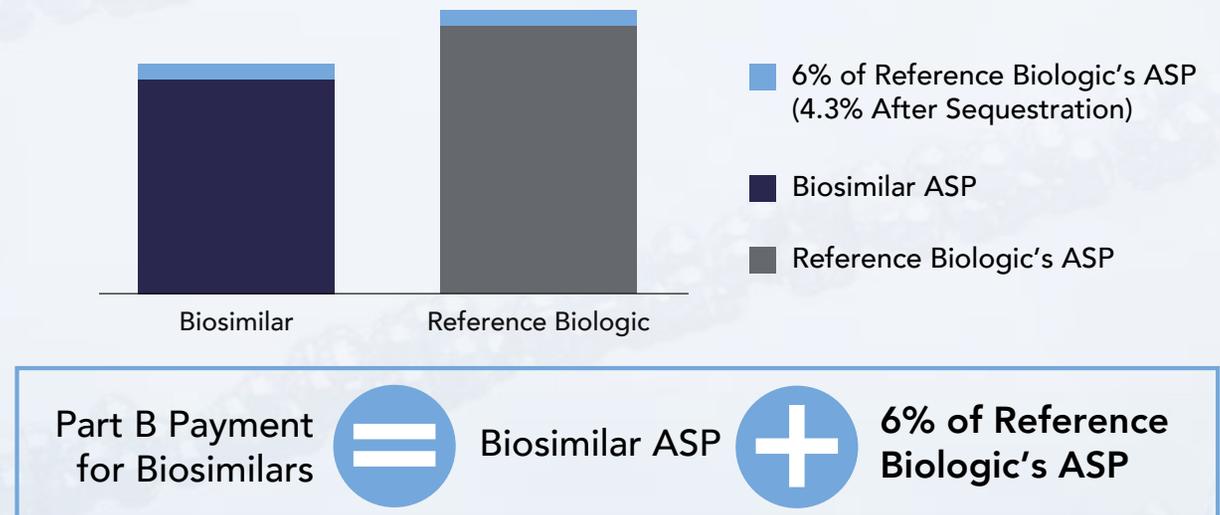
Biosimilars may be covered under the medical benefit or the pharmacy benefit.<sup>109</sup> Self-administered medicines (often delivered by a specialty pharmacy) are typically covered under the pharmacy benefit, while those injected or infused under the supervision of a physician are typically paid for under the medical benefit.<sup>110</sup> As of December 2018, most of the biosimilars marketed in the US are covered under the medical benefit by payers, although they may also be covered under the pharmacy benefit, especially when managed through specialty pharmacies.

## Medical Benefit

As of January 2018, CMS assigned each biosimilar a unique HCPCS code, and its average selling price (ASP) will not be combined with those of other biosimilars.<sup>111</sup> This is a positive change from previous billing and coding policy that grouped biosimilars with a common reference product in the same HCPCS code,<sup>112</sup> as biosimilars and reference products now operate on a level playing field in terms of coding.

The ACA included language to create a level playing field between reference products and biosimilars. As shown in **Figure 4**, Medicare Part B reimburses physicians for biosimilars at the biosimilar's ASP plus 6% (4.3% after sequestration) of the reference biologic's ASP.<sup>19,80</sup> In other words, Congress kept the field level by providing physicians the same add-on amount regardless of whether they prescribe a reference product or a biosimilar. This allows all manufacturers to compete on equal terms.

**Figure 4. Medicare Part B Reimbursement for Biosimilars**



Key: ASP – average selling price.

As of January 2019, because there is often a 2-calendar quarter lag from this time when a product launches until its ASP is published, Medicare reimburses Part B drugs—including biosimilars—based on their WAC plus a 3% add-on of the biosimilar’s WAC until the ASP figures become available. Once the ASP data are available, Medicare reimburses biosimilars using the ASP methodology (ASP plus 6% of the reference product’s ASP).

**Table 4** shows hypothetical examples of physician office or community clinic and outpatient payments for a biosimilar under Medicare Part B.<sup>113</sup>

**Table 4. Payment Methodology for Biosimilars Under Medicare Part B<sup>111,113</sup>**

Biologic Product	Reference Product	Biosimilar A	Biosimilar B
WAC (list price)	\$1,000.00	\$800.00	\$700.00
ASP*	\$800.00	\$640.00	\$560.00
6% of Reference Product’s ASP	\$48.00		
Payment Rate (ASP + 6%) (before sequestration)	\$848.00	\$688.00	\$608.00
Payment Rate (ASP + 4.3%) (after sequestration)	\$834.40	\$674.40	\$594.40
Patient Cost-Share (20%)†	\$169.60	\$137.60	\$121.60

\* Note: This hypothetical example assumes that the biologics’ (both reference and biosimilar) ASPs are 20% less than the WAC based on rebates over time.

† Sequestration lowers the 80% Medicare payment to physicians by 2%, but the beneficiary copayment remains at 20% of the original payment rate of ASP+6%.

Key: ASP – average sales price; WAC – wholesale acquisition cost.

## 340B Program

The 340B program requires pharmaceutical manufacturers participating in Medicaid to sell outpatient drugs at discounted prices to healthcare organizations that provide care for many uninsured and low-income patients. These organizations include community health centers, children's hospitals, hemophilia treatment centers, critical access hospitals, sole community hospitals, rural referral centers, and public and nonprofit disproportionate share hospitals that serve low-income and indigent populations.<sup>114</sup> Sites within a healthcare system that qualify as 340B entities can obtain federally mandated "ceiling price" discounts for covered outpatient drugs, while other sites that are not eligible pay a higher net price.<sup>115</sup>

Before January 1, 2018, Medicare paid both 340B and non-340B hospitals at the same rate for certain 340B treatments, such as biologicals (including biosimilars), even though 340B hospitals can obtain those treatments at a discount.<sup>116</sup> Effective January 1, 2018, however, CMS changed the Medicare Part B hospital outpatient department payment methodology for 340B drugs. In the hospital outpatient department setting, CMS assigns pass-through status to qualifying new drugs and biologics—including biosimilars—which lasts for at least 2 years but not more than 3 years.<sup>117</sup> Medicare now pays for non-pass-through drugs and biologics (other than vaccines) purchased through the 340B program at ASP minus 22.5%.<sup>118</sup> (This reduced payment methodology is now in question, due to a lawsuit brought by the American Hospital Association and others, as discussed below.)

### Developing Story<sup>119</sup>

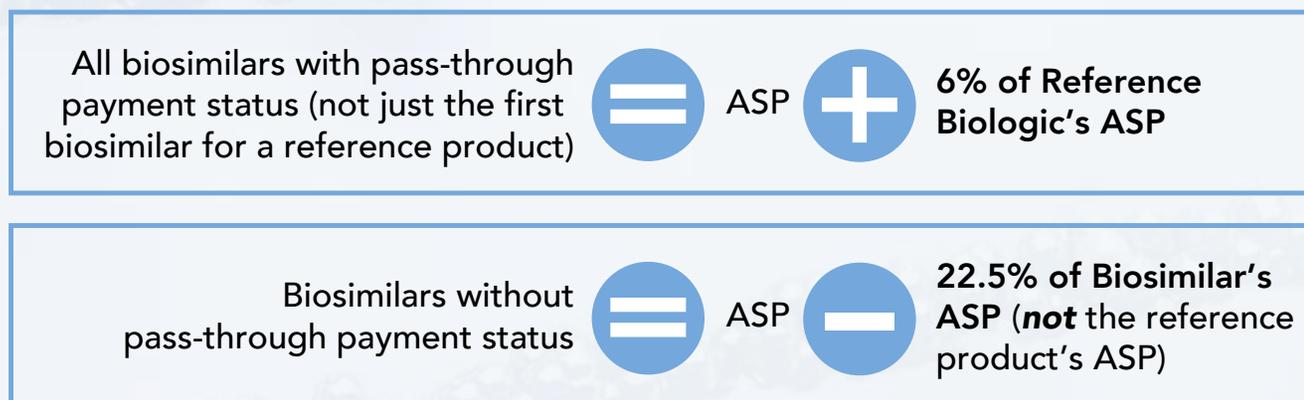
When CMS finalized its rule in November 2017 to have Medicare reimburse hospitals for drugs purchased under the 340B program at ASP minus 22.5%, the American Hospital Association, the Association of American Medical Colleges, and America's Essential Hospitals filed a lawsuit to prevent the payment cuts.

In December 2018, a district judge for the District of Columbia agreed with the hospital groups, ruling that CMS overstepped its regulatory authority. However, the court did not issue a remedy, such as an injunction, but instead requested briefing by the parties regarding the appropriate remedy. As of February 2019, this issue is ongoing.

For calendar year 2019, CMS continues its current policy to make all biosimilars eligible for pass-through payment, not just the first biosimilar for a reference product.<sup>120</sup>

Additionally, CMS adopted a policy that any biosimilar with pass-through payment status will be exempt from Medicare's alternative payment methodology for 340B drugs (ie, ASP minus 22.5%).<sup>120</sup> The box below describes Medicare reimbursement for biosimilars under the 340B program.

### **Medicare Reimbursement for Biosimilars Under the 340B Program<sup>120</sup>**



**Table 5** on the next page shows an example of a comparison of reference biologic and biosimilar Part B reimbursement in the hospital outpatient department.<sup>120</sup> The Medicare payment amounts for products under the 340B Drug Pricing Program change quite a bit, depending on the product's pass-through payment status. As of 2018, both the provider's payment and the patient's cost-share vary appreciably, depending on the biological product being prescribed and administered under the 340B Drug Pricing Program.

Decision makers in hospitals and health systems should ensure awareness of any differences between a biosimilar and its reference product, as well as biosimilars with and without pass-through payment status, with respect to the 340B Drug Pricing Program.

**Table 5. Hospital Outpatient Department Payment Methodology for 340B Reference Biologics and 340B Biosimilars in Medicare Part B<sup>120</sup>**

Biologic Product	Reference Product	Biosimilar A, <u>With</u> Pass-Through Status	Biosimilar A, <u>Without</u> Pass-Through Status
WAC (List Price)	\$1,000.00	\$800.00	\$800.00
ASP*	\$800.00	\$640.00	\$640.00
6% of Reference Product's ASP	N/A	\$48.00	N/A
22.5% of its Own ASP	\$180.00	N/A	\$144.00
Hospital Outpatient Payment Rate (before sequestration)	\$620.00	\$688.00	\$496.00
Hospital Outpatient Payment Rate (after sequestration)	\$610.08	\$676.99	\$488.06
Patient Cost-Share (20%)	\$124.00	\$137.60	\$99.20

\* Note: This hypothetical example assumes that the biologics' (both reference and biosimilar) ASPs are 20% less than the WAC based on rebates over time.  
Key: ASP – average sales price; WAC – wholesale acquisition cost.

## Pharmacy Benefit

Most biosimilars are covered under the medical benefit; however, many are also covered under the pharmacy benefit, especially when administered by specialty pharmacies.

It is not necessary for biosimilars to have preferred formulary status to foster uptake; rather, it is more important to have parity coverage between biosimilars and reference products. Preferential policies can cause market distortions that inhibit robust market competition, putting long-term healthcare system savings at risk. However, as shown in **Figure 5**, an Avalere study in May 2018 of 18 of the top 25 US commercial payers showed a supportive-care biosimilar being preferred by more plans than the reference biologic.<sup>121</sup>

Biosimilar uptake can be achieved by manufacturers that are committed to market competition, which will create savings for patients and the healthcare system. Just as with reference products, biosimilars will compete not only on price but on a wide range of attributes, including product qualities, patient services, and provider education and support.

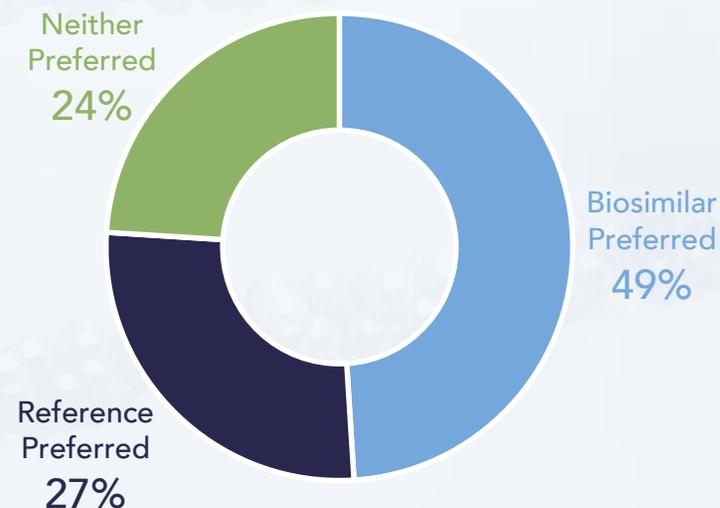
As shown in **Figure 6**, the Medicare Part D standard benefit is divided into 4 phases of coverage: deductible, initial coverage, coverage gap (“donut hole”), and catastrophic coverage.<sup>122</sup>

To limit patient out-of-pocket costs, Congress created the Coverage Gap Discount Program as part of the ACA, which aimed to eliminate the coverage gap over time.<sup>123</sup> The Coverage Gap Discount Program manages subsidies differently for brand and generic drugs.<sup>124</sup>

One significant change from Congress is that Medicare Part D now treats biosimilars the same as reference products. As a result, biosimilar manufacturers will join brand name pharmaceutical manufacturers in contributing 70% to patients’ donut-hole expenses.<sup>125</sup>

In 2019, after paying a \$415 deductible, beneficiaries have a 25% copayment for brand name drugs and biologics (including biosimilars) until they reach catastrophic coverage. After the deductible, beneficiaries spend another \$1,809.69 out of pocket to reach catastrophic coverage, where they have a 5% copayment with no spending ceiling. Including the deductible, beneficiaries will have spent \$2,224.69 out of pocket to reach catastrophic coverage in 2019.

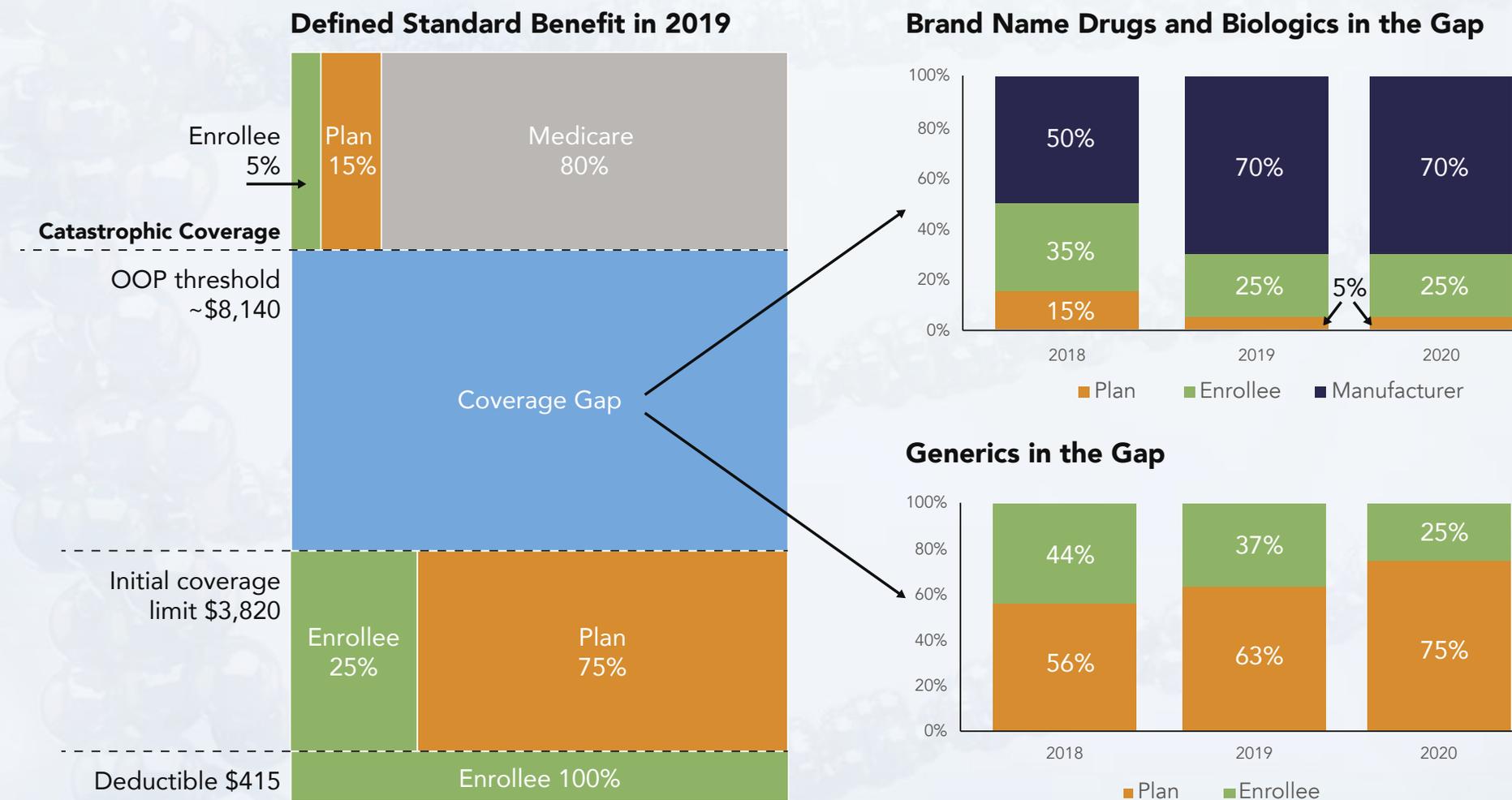
**Figure 5. Proportion of Lives Covered With Available Formularies Under the Pharmacy Benefit<sup>121</sup>**



Note: 18 commercial payers (172 million covered lives), May 2018.

**Figure 6. 2019 Part D Standard Benefit Design<sup>122</sup>**

As of 2019, cost-sharing for brand name drugs in the coverage gap is 25%



Key: OOP – out-of-pocket.

CMS has modified the definition of generic drugs in 2019, for the purposes of the non-Low-Income Subsidy (non-LIS) catastrophic and LIS cost-sharing, to include biosimilar therapies.<sup>126</sup> Starting in 2019, CMS considers biosimilars to be generic drugs for LIS cost-sharing and non-LIS catastrophic cost-sharing, so beneficiaries will not have to pay more expensive brand copayments. **Table 6** below highlights the change in copay amounts that Part D enrollees will have to pay.

**Table 6. Change in Part D Copayments for Biosimilars<sup>127</sup>**

	2018 Copay	2019 Copay
<b>LIS beneficiaries ≤100% FPL</b>	\$3.70 ( <i>brand</i> )	\$1.25 ( <i>generic</i> )
<b>LIS beneficiaries &gt;100% FPL</b>	\$8.35 ( <i>brand</i> )	\$3.40 ( <i>generic</i> )
<b>Non-LIS beneficiaries in catastrophic coverage</b>	\$8.35 ( <i>brand</i> )	\$3.40 ( <i>generic</i> ) or 5% coinsurance, whichever is greater <sup>128</sup>

Key: CMS – Centers for Medicare and Medicaid Services; FPL – Federal Poverty Level; LIS – Low-Income Subsidy.

## Medicaid

In December 2016, CMS issued a notice reinforcing its position that biosimilars do not qualify as authorized generic drugs for the purpose of the Medicaid Drug Rebate Program and are subject to brand-level rebates. The notice adds that the “best price of the reference biologic and the biosimilar biologic should be determined separately as the lowest price available from each manufacturer.”<sup>129</sup>



# LOOK TO THE HORIZON

# Look to the Horizon

Confidence in biosimilars from patients, physicians, and payers depends on regulators maintaining scientifically appropriate standards for demonstrating biosimilarity and interchangeability, while ensuring patient safety and efficacy.

A greater market share of biosimilars compared to reference products is not the only measure of success—competition that leads to savings is most important, whether providers and payers continue to choose reference products or biosimilars.

In 2018, the US released more regulatory policies to support the use of biosimilars, focusing on competition that will lead to savings. The policies that help lay the groundwork for rapid growth of biosimilars in the market over the next couple of years included the following:

- The FDA's announcement of the Biosimilars Action Plan (BAP) showed the agency's commitment to ensuring the US has a robust biosimilar market. The BAP's central thesis is that competition can and should be leveraged to reduce drug prices.<sup>18</sup>
  - The BAP applies many lessons the FDA learned from its experience with generic drugs to accelerate biosimilar competition, distilled into the following key goals:<sup>18</sup>

Improving the efficiency of the biosimilar and interchangeable product development and approval process

Maximizing scientific and regulatory clarity for the biosimilar product development community

Developing effective communications to improve understanding of biosimilars among patients, clinicians, and payers

Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition

- In May 2018, the Department of Health and Human Services released *American Patients First: The Trump Administration Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs*, a far-reaching proposal to address challenges in the American drug market. The blueprint discussed:<sup>130</sup>
  - Improving competition by promoting the use of biosimilars
  - The administration's actions to assign each biosimilar for a given biologic its own billing and payment code under Medicare Part B
  - The FDA's plans to issue new policies to improve the availability, competitiveness, and adoption of biosimilars as affordable alternatives to branded biologics
  - The FDA's plans to educate clinicians, patients, and payers about biosimilar and interchangeable products, and increase their awareness

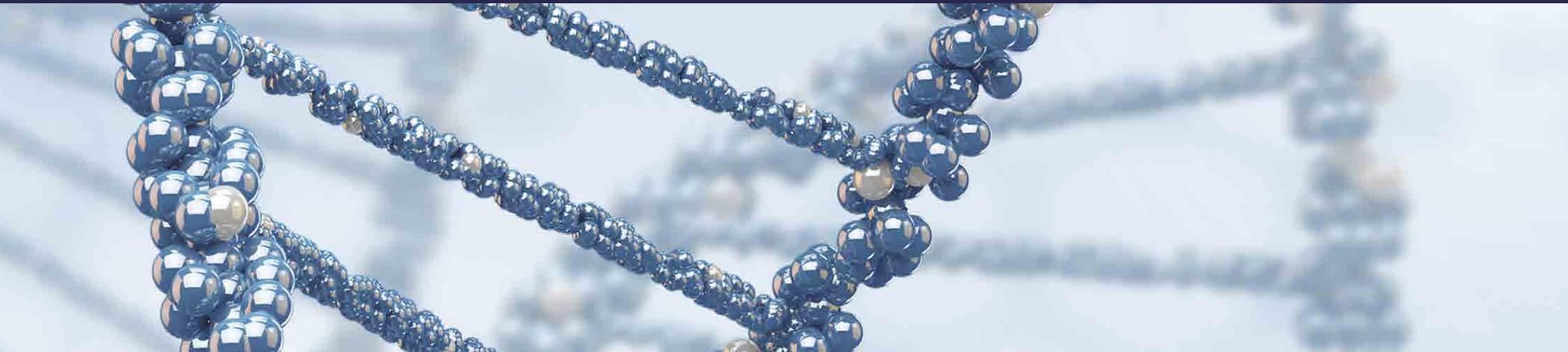
The BAP includes an action item to improve the “Purple Book” that lists biological products, including any biosimilar and interchangeable biological products licensed by the FDA under the Public Health Service Act.<sup>131</sup>

- The enhanced Purple Book will include more information about approved biological products; will provide a modernized, interactive user experience; and will publish information about newly approved or withdrawn biological license applications and reference-product exclusivity determinations.<sup>131</sup>
- When released, the revised “Purple Book” will be a valuable resource for healthcare providers, payers, and researchers, especially as the number of approved biosimilar and interchangeable products increases.

These regulatory policies, and more likely to come this year, will lead to increased confidence of patients, providers, and payers to use biosimilars based on clinically accurate and easy-to-understand educational efforts by regulators, patient groups, and providers. Improved competition will potentially lead to cost savings for the US health system. In turn, this can promote increased innovation from reduced spending. Most importantly, stakeholders support the use of biosimilars because the savings and innovation lead to additional options for patients.

There are many exciting developments in the biosimilar market. Biosimilars are poised to make a big impact in the healthcare marketplace with potential economic and health benefits for patients. Sound, science-based policies that support market competition and confidence from patients, physicians, pharmacists, and payers will promote a robust and sustainable US biosimilar market.

For additional information on biosimilars, please visit [www.amgenbiosimilars.com](http://www.amgenbiosimilars.com).

A close-up photograph of a blue beaded necklace with several strands of small, round, metallic-looking blue beads. The necklace is draped and the background is blurred.

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