Dear Colleagues,

The biosimilars landscape is entering a time of remarkable change. As of early 2020, there are 18 biosimilar products that have launched in the United States (US) and many have gained significant share in the therapeutic area where they were introduced. Sustaining this growth is critical and dependent upon maintaining appropriate regulatory and competitive mechanisms to promote a level playing field for all biologics.

The combination of our 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.1,2

As an active participant in the ongoing national discussion, we are pleased to share with you the seventh edition of our Biosimilars Trend Report. The 2020 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.*

*Throughout this report, unless otherwise noted, the term “biosimilars” refers to biological products licensed under 351(k) of the Public Health Service Act.

Kave Niksefat
Vice President
US Value and Access, Amgen
When the Biologics Price Competition and Innovation Act (BPCIA) was enacted in the US in 2010, creating the biosimilars approval pathway, we embraced the opportunity to extend our mission to serve patients. We recognized that biosimilars would become an important part of broadening patient and physician options for biologic treatments and foresaw that our expertise in developing and manufacturing biologics would also apply to biosimilars.

Starting with that premise, we have invested more than $2 billion across our portfolio of 10 biosimilar candidates and marketed products intended to target serious diseases. We have reached a unique position—we have a deep and growing portfolio of innovator products, as well as an already-successful commitment to developing and marketing biosimilars. With multiple US approvals and launches of biosimilars, we have a far larger stake than most companies entering the marketplace with biosimilars.

Our high-quality biosimilars can potentially offer more affordable, life-altering treatment options that contribute to the sustainability of our healthcare system and allow for greater investment in new medicines for patients. We also have unique insights and a commitment to advocate for a biologics marketplace that will promote innovation and quality, while at the same time bringing more competition and meaningful cost savings to the healthcare system.
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EXECUTIVE SUMMARY
EXECUTIVE SUMMARY

Since the first biosimilar entered the US marketplace in 2015, 28 products have been approved and 18 products have been launched. Biosimilars have gained significant share in the majority of therapeutic areas where they have been introduced.3–7

The US marketplace is poised to welcome many new biosimilars in 2020 and beyond, spurring additional competition that will potentially lead to significant savings for the healthcare system, and these savings can be deployed to newer, innovative treatments.7,8

The last year has seen a 65% jump in the number of approved biosimilars and a 157% increase in available biosimilars.3–6

Many competitive mechanisms are in place to support biosimilar uptake. For example, the Centers for Medicare and Medicaid Services (CMS) have established separate Healthcare Common Procedure Coding System (HCPCS) codes and payment rates for biosimilars, treating them similarly to other biologics, which supports their uptake and can help lead to meaningful cost savings and a sustainable marketplace.8,9

Current US regulatory standards for developing and approving biosimilars, as well as for establishing interchangeability, are scientifically appropriate to protect patient safety and support provider and payer confidence.10–12 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 clinical, economic, and operational needs and decision-making drivers.12–14

Essential components of provider and patient use of biosimilars include addressing the clinical, economic, and operational considerations relevant to adoption as well as payer coverage.15–19

Biosimilar adoption is not the only measure of success. With more biosimilars available, reference products may lower prices to compete.20
CURRENT STATE OF THE MARKETPLACE
The US marketplace is poised to welcome many new biosimilars in 2020 and beyond, spurring additional competition that will potentially lead to significant savings for the healthcare system, which can then be deployed to newer, innovative treatments.\(^7,8\)

Over the past couple of years, the US regulatory agencies have developed policies that maintain a level playing field for biosimilars and reference products. The FDA’s 2018 Biosimilars Action Plan has injected energy into the system, and CMS policies are supporting the prescribing of biosimilars.

Essential components of provider and patient use of biosimilars include addressing the clinical,\(^15\) operational,\(^17\) and economic\(^16\) considerations to drive adoption as well as payer coverage.\(^18,19\)

Biosimilar adoption is one of many measures of success. Reference products may also lower prices to compete. This is a positive outcome that results from biosimilar competition.\(^20\)

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 clinical, economic, and operational needs and decision-making drivers.\(^12-14\)

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**Sean McGowan, Senior Director of Biosimilars, AmerisourceBergen**

*Fortunately, there has been more momentum on the biosimilar front in the last 6 months than ever before. Of the 15 products officially launched in the US [at the time this was written], more than half of them launched in the last year. And for the first time in the US, there are 3 biosimilars competing in both the Neulasta and Herceptin markets. Despite headlines that the biosimilar market has not delivered on its promise, the latter half of 2019 indicates that the market is heating up.*\(^21\)
The US marketplace for biosimilars is now well established and accelerating across multiple therapeutic areas. In 2018, the FDA approved 7 biosimilars, which brought the total approvals to 16. In 2019, the FDA approved 10 biosimilars, bringing the total number of approved biosimilars to 26 in the US. Figure 1 shows the number of biosimilars approved each year from 2015 to 2020. The steadily increasing number shows the growing strength of US biosimilars. As of July, the FDA has approved 2 biosimilars in 2020. The COVID-19 pandemic and the resulting shutdown of many businesses most likely contributed to the slowdown of biosimilar approvals.

In addition, more biosimilars are becoming available to patients. By the end of 2018, there were only 3 biosimilars. In 2019, however, 6 became available, followed by another 6 in the first 7 months of 2020. Figure 2 shows the dramatic increase in available biosimilars in 2019 and 2020 compared to prior years.

*2020 totals only include January to July.
CURRENT STATE OF THE MARKETPLACE

Comparison to the EU

Current data show that the US biosimilar landscape is advancing faster than the EU biosimilar landscape during a comparable period of time. In the 5 years after the EU approved the first biosimilar (2006), there were a total of 11 approved biosimilars. By contrast, in the first 5 years after the US approved the first biosimilar, there were a total of 26 approved biosimilars—more than twice the number in the EU. Figure 3 shows that, by the end of Year 5, Europe had 11 biosimilars approved and the US had 26.3,22

Figure 3. Comparison of Approved Biosimilars in Europe and the US3,22
Cumulative Number of Biosimilars Approved for Marketing in Europe vs the US, Beginning With Year the First Biosimilar Was Approved
CURRENT STATE OF THE MARKETPLACE

Timeline of Approved Biosimilars and Launch Date

As of July 2020, the FDA has approved 28 biosimilars and 18 biosimilars have been launched in the US as shown in Figure 4. Currently, there are 9 reference products that have approved biosimilars, of which 7 are available.3–6

Figure 4. Approved and Launched Biosimilars (including GRANIX*) in the US3-6,23,24

Key: FDA – Food and Drug Administration.
*GRANIX is not a biosimilar. It was approved under a full Biologics License Application, which was submitted to the FDA before enactment of the biosimilar approval pathway.

Please click here for Boxed Warning information for KANJINTI, AVSOLA, EPOGEN and Enbrel.
Figure 4. Approved and Launched Biosimilars (including GRANIX*) in the US³–⁶,2³,2⁴
Growth in Biosimilar Approval and Availability

Of the biosimilars approved to date in 2020, 64% have launched and are available to patients.\(^3\)\(^-\)\(^6\)

The last year has seen a notable increase in the approval and availability of biosimilars.\(^3\)\(^-\)\(^6\)

As evidenced from the adoption of biosimilars in Europe over the last 13 years, manufacturers, payers, and providers in the US expect biosimilar competition will potentially lead to consistent price reduction.\(^2\)\(^5\) These savings can be invested in spending for new, innovative medicines.

Policy Changes That Have Impacted the Marketplace

The US regulatory environment is evolving to support the uptake of biosimilars. For example, CMS has made important changes to the current US reimbursement system, such as establishing separate HCPCS codes and payment rates for biosimilars. These changes, along with others, help to level the playing field between biosimilars and reference products, which will lead to increased competition and help to support a sustainable marketplace.\(^2\)\(^6\)
**CURRENT STATE OF THE MARKETPLACE**

**Biosimilars Launch With Significant Discounts to WAC and ASP**

Biosimilars are reducing healthcare costs by providing significant wholesale acquisition cost (WAC) and average sales price (ASP) savings at launch and through price competition, resulting in additional savings over time. As shown in Figur e 5, manufacturers are launching biosimilars at a WAC price that is generally 15% to 37% lower than the reference product WAC, and almost all biosimilar manufacturers are launching at a WAC price that is 3% to 24% below the reference product ASP.27 (Biosimilars’ ASP becomes available 2 full quarters after launch.)

**Figure 5. Price at Launch vs Reference Product**

<table>
<thead>
<tr>
<th></th>
<th>Bio WAC vs RP WAC</th>
<th>Bio WAC vs RP ASP</th>
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<tbody>
<tr>
<td>Filgrastim</td>
<td></td>
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<tr>
<td>ZAR-X® (11/10)</td>
<td>-12%</td>
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<td>Nevasyn® (10/18)</td>
<td>24%</td>
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<td>Infliximab</td>
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<td>Inflectra® (11/16)</td>
<td>-13%</td>
<td>3%</td>
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<td>AVSOLA® (7/17)</td>
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<tr>
<td>Pegfilgrastim</td>
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<tr>
<td>Fujithala® (7/16)</td>
<td>31%</td>
<td>4%</td>
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<tr>
<td>UDENYCA® (7/16)</td>
<td>33%</td>
<td>5%</td>
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<tr>
<td>ZEZELEN® (12/16)</td>
<td>-37%</td>
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<tr>
<td>Epoetin Alfa (EPOGEN®)</td>
<td>20%</td>
<td>5%</td>
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<tr>
<td>Retacrit® (9/18)</td>
<td>33%</td>
<td>5%</td>
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<tr>
<td>Epoetin Alfa (PROCRIT®)</td>
<td>20%</td>
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<tr>
<td>Retacrit® (9/18)</td>
<td>33%</td>
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<td>Trastuzumab</td>
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<td>Herceptin® (3/20)</td>
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<td>Ontuxint® (4/20)</td>
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<td>Bevacizumab</td>
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<td>MIVAF (7/19)</td>
<td>15%</td>
<td>12%</td>
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<tr>
<td>Ziraxel™ (1/20)</td>
<td>23%</td>
<td>9%</td>
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<tr>
<td>Rituximab</td>
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<tr>
<td>Trasimuno® (7/11)</td>
<td>30%</td>
<td>3%</td>
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<tr>
<td>Rentice® (1/20)</td>
<td>24%</td>
<td>20%</td>
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Key: ASP – average sales price; bio – biosimilar; RP – reference product; WAC – wholesale acquisition cost.

*GRANIX is not a biosimilar. It was approved under a full Biologics License Application, which was submitted to the FDA before enactment of the biosimilar approval pathway.

Source: Analysource.

Please [click here](#) for Boxed Warning information for KANJINTI, AVSOLA, EPOGEN, and Enbrel.
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<td>-23%</td>
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<tr>
<td>ZARXIO® (9/15)</td>
<td>-15%</td>
<td>3%</td>
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<td>Nivestym® (10/18)</td>
<td>-34%</td>
<td>-24%</td>
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<tr>
<td><strong>Infliximab</strong></td>
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<tr>
<td>Inflectra® (11/16)</td>
<td>-15%</td>
<td>4%</td>
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<tr>
<td>RENFLEXIS® (7/17)</td>
<td>-35%</td>
<td>7%</td>
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<tr>
<td>AVSOLA™ (7/20)</td>
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<td>-6%</td>
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<td><strong>Pegfilgrastim</strong></td>
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<td>UDENYCA* (1/19)</td>
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<tr>
<td>ZIEKTENZO® (12/19)</td>
<td>-37%</td>
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<td>Retacrit® (9/18)</td>
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<td><strong>Trastuzumab</strong></td>
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<tr>
<td>KANJINTI® (7/19)</td>
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<td>Ogivri® (12/19)</td>
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<td>Trazimera™ (2/20)</td>
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<td>HERZUMA® (3/20)</td>
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<td>Truxima® (11/19)</td>
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<td>5%</td>
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<tr>
<td>Ruxience™ (1/20)</td>
<td>-24%</td>
<td>-20%</td>
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Key: ASP – average sales price; bio – biosimilar; RP – reference product; WAC – wholesale acquisition cost.
*GRANIX is not a biosimilar. It was approved under a full Biologics License Application, which was submitted to the FDA before enactment of the biosimilar approval pathway.
Source: Analysource.
ASP of Reference Products are Declining

As expected, competition results in lower ASP for both reference products and biosimilars, leading to additional savings. As shown in Figure 6, in most cases, the prices of biosimilars decline once ASP is established and continue a steady downward trend. The ASPs for reference products are also declining over time, leading to further healthcare savings.

Figure 6. Downward Trend in ASP for Biosimilars and Reference Products Over Time

Cost-Savings in Biosimilar vs Reference Product

Please click here for Boxed Warning information for KANJINTI, AVSOLA, EPOGEN and Enbrel.

Key: ASP – average sales price.
Note: With a launch date of July 2020, AVSOLA™ data are unavailable at time of comparison and excluded from figure.
*NEUPOGEN®’s biosimilar price-response strategy focused on account level provider contracting. This targeted approach modestly increased the ASP-eligible discount rate resulting in a more stable ASP trend.
Source: Analysource.
Figure 6. Downward Trend in ASP for Biosimilars and Reference Products Over Time

Cost-Savings in Biosimilar vs Reference Product

Change in Reference Product and Biosimilar Price, Following Biosimilar Launch

Quarters Since Biosimilar Launch

Key: ASP – average sales price.
Note: With a launch date of July 2020, AVSOLA™ data are unavailable at time of comparison and excluded from figure.
*NEUPOGEN®'s biosimilar price-response strategy focused on account level provider contracting. This targeted approach modestly increased the ASP-eligible discount rate resulting in a more stable ASP trend.
Source: Analysource.
Growth in Biosimilar Uptake

The rate of biosimilar uptake is generally increasing over time, as depicted in Figure 7. Biosimilars have gained significant share in the majority of therapeutic areas where they have been introduced. Within the first year, biosimilar share generally ranged from 20% to 25%. The share of NEUPOGEN biosimilars is almost 75% after 5 years. Additionally, first-to-launch biosimilars tend to capture a greater portion of the segment compared to later entrants.

Figure 7. Biosimilars Growth Uptake Curve

*Q2’20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar. With a launch date of July 6, 2020, AVSOLA™ data are unavailable at time of comparison and excluded from figure. Source: OBU Customer Data Pack Weekly (IQVIA DDD + Chargeback).
Figure 7. Biosimilars Growth Uptake Curve

*Q2’20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar. With a launch date of July 6, 2020, AVSOLA™ data are unavailable at time of comparison and excluded from figure.

**BOXED WARNINGS**

**EPOGEN®**

**WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE**

See Full Prescribing Information for complete risk information.

**Chronic Kidney Disease:**
- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL (5.1).
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
- Use the lowest EPOGEN® dose sufficient to reduce the need for red blood cell (RBC) transfusions (5.1).

**Cancer:**
- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (Table 2, 5.2).
- To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions (2.4).
- Use ESAs only for anemia from myelosuppressive chemotherapy (1.3).
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure (1.5).
- Discontinue following the completion of a chemotherapy course (2.4).

**Perisurgery:**
- Due to increased risk of Deep Venous Thrombosis (DVT), DVT prophylaxis is recommended (5.1).

**Enbrel®**

**WARNINGS: SERIOUS INFECTIONS AND MALIGNANCIES**

See Full Prescribing Information for complete risk information.

**SERIOUS INFECTIONS**
- Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. (5.1)
- Enbrel should be discontinued if a patient develops a serious infection or sepsis during treatment. (5.1)
- Perform test for latent TB; if positive, start treatment for TB prior to starting Enbrel. (5.1)
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)

**MALIGNANCIES**
- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including Enbrel. (5.3)
BOXED WARNINGS (cont.)

KANJINTI®

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

See Full Prescribing Information for complete risk information.

Cardiomyopathy: Trastuzumab products can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue KANJINTI for cardiomyopathy. (2.3, 5.1)

Infusion Reactions, Pulmonary Toxicity: Discontinue KANJINTI for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. (5.2, 5.4)

Embryo-Fetal Toxicity: Exposure to trastuzumab products during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Advise patients of these risks and the need for effective contraception. (5.3, 8.1, 8.3)

AVSOLA™

WARNING: SERIOUS INFECTIONS and MALIGNANCY

See Full Prescribing Information for complete risk information.

- Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis) and infections due to other opportunistic pathogens.
- Discontinue AVSOLA if a patient develops a serious infection.
- Perform test for latent TB; if positive, start treatment for TB prior to starting AVSOLA. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)
- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, including infliximab products.
- Postmarketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF-blockers including infliximab products. Almost all had received azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of cases were reported in patients with Crohn’s disease or ulcerative colitis, most of whom were adolescent or young adult males. (5.2)
TRENDS

ONCOLOGY THERAPEUTICS

ONCOLOGY SUPPORTIVE CARE

NEPHROLOGY/ONCOLOGY SUPPORTIVE CARE

INFLAMMATION
TRENDS

ONCOLOGY THERAPEUTICS

ONCOLOGY SUPPORTIVE CARE

NEPHROLOGY/ONCOLOGY SUPPORTIVE CARE

INFLAMMATION

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TRENDS

ONCOLOGY THERAPEUTICS

ONCOLOGY SUPPORTIVE CARE

NEPHROLOGY/ONCOLOGY SUPPORTIVE CARE

INFLAMMATION

KEY CONSIDERATIONS

REIMBURSEMENT

POLICY CONSIDERATIONS

BIOSIMILARS IN REVIEW

REFERENCES
The biosimilars available for oncology therapeutics consist of trastuzumab, bevacizumab, and rituximab. For each, we discuss:

1. WAC and ASP of the biosimilar at launch compared to the reference product
2. ASP for the reference product and biosimilars since launch
3. Biosimilar uptake

Biologics account for half of the pharmacological products in oncology; however, their high cost is a result of greater costs of development and production compared to small molecules.30 Biosimilars can help drive down that high cost with 12 becoming available to patients in 2019 and 2020 (as of July).3–6

As this section demonstrates, biosimilars available for oncology therapeutics have exhibited strong growth. For example, both trastuzumab and bevacizumab biosimilars account for at least 40% of sales by volume. The rituximab biosimilars are comparatively newer, though they still account for 20% of sales by volume.29

“We have to address the problem of cancer drug costs, and biosimilars may help us.”31

– Sara Hurvitz, MD, associate professor at the David Geffen School of Medicine at UCLA; medical director of the Jonsson Comprehensive Cancer Center Clinical Research Unit; co-director of the Santa Monica-UCLA Outpatient Oncology Practices; and director of the Breast Cancer Clinical Trials Program at UCLA
ONCOLOGY THERAPEUTICS

Trastuzumab

Five trastuzumab biosimilars have launched since 2019 to compete with the reference product Herceptin (trastuzumab):

<table>
<thead>
<tr>
<th>Brand</th>
<th>WAC Discount</th>
<th>ASP Discount</th>
</tr>
</thead>
<tbody>
<tr>
<td>KANJINTI®</td>
<td>15%</td>
<td>13%</td>
</tr>
<tr>
<td>Ogivri®</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>Trazimera™</td>
<td>22%</td>
<td>19%</td>
</tr>
<tr>
<td>Herzuma®</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Ontruzant</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Launched at a Price

Please click here for Boxed Warning information for KANJINTI.
See Full Prescribing Information for complete risk information.
Trastuzumab

As Figure 8 shows, all 5 biosimilars launched at WAC and ASP discounts to the reference product with some launching at discounts below their predecessors.

Figure 8. WAC and ASP of Trastuzumab Biosimilars Relative to Reference Product at Launch

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

*ASP not available for these products at time of comparison. WAC price is used to compare with reference product ASP.

Source: Analysource.

Please click here for Boxed Warning information for KANJINTI. See Full Prescribing Information for complete risk information.

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

*ASP not available for these products at time of comparison. WAC price is used to compare with reference product ASP.

Source: Analysource.
Figure 8. WAC and ASP of Trastuzumab Biosimilars Relative to Reference Product at Launch

<table>
<thead>
<tr>
<th>WAC Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q3'19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product</th>
<th>WAC</th>
<th>ASP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herceptin</td>
<td>$4,364</td>
<td>$3,697</td>
</tr>
<tr>
<td>KANJINTI</td>
<td>$3,697</td>
<td>$3,697</td>
</tr>
<tr>
<td>Ogivri</td>
<td>$3,697</td>
<td>$3,697</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WAC Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q3'19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product</th>
<th>WAC</th>
<th>ASP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herceptin</td>
<td>$4,129</td>
<td>$3,192</td>
</tr>
<tr>
<td>KANJINTI</td>
<td>$3,697</td>
<td>$3,391</td>
</tr>
<tr>
<td>Ogivri</td>
<td>$3,697</td>
<td>$3,927</td>
</tr>
</tbody>
</table>

Key: ASP – average sales price; WAC – wholesale acquisition cost.
*ASP not available for these products at time of comparison. WAC price is used to compare with reference product ASP.
Source: Analysource.
Trastuzumab

Figure 9 shows the percentage change in the price of biosimilars over time, when compared to the reference product’s ASP at the time that the first trastuzumab biosimilar launched. Trastuzumab biosimilars all launched at a price 7%–20% lower than the reference product Herceptin’s ASP at the time of the first biosimilar launch.

Figure 9. ASP of Trastuzumab Products at Biosimilars’ Launches

Please click here for Boxed Warning information for KANJINTI. See Full Prescribing Information for complete risk information.

Key: ASP – average sales price.
*Q2’20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar.
Biosimilar WAC price used for comparing against reference product ASP until biosimilar ASP is available.
Source: Analysource.
ONCOLOGY THERAPEUTICS

Trastuzumab

As seen in Figure 10, there has been a strong adoption of trastuzumab biosimilars. KANJINTI captured 33% share within 12 months, while Ogivri captured 5% in its first 2 quarters of availability. HERZUMA and Ontruzant had just launched at the time of publication, so their share was negligible.

Figure 10. Biosimilar Uptake Curve for Trastuzumab Products^9

Please click here for Boxed Warning information for KANJINTI.
See Full Prescribing Information for complete risk information.

^Q2'20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar. Source: OBU Customer Data Pack Weekly (IQVIA DDD + Chargeback).
Since 2019, two bevacizumab biosimilars have launched to compete with the reference product Avastin (bevacizumab):

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Launched at a Price&lt;sup&gt;27&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVASI&lt;sup&gt;®&lt;/sup&gt;</td>
<td>15% less than Avastin’s WAC</td>
</tr>
<tr>
<td>Zirabev&lt;sup&gt;™&lt;/sup&gt;</td>
<td>23% less than Avastin’s WAC</td>
</tr>
</tbody>
</table>
As Figure 11 shows, in addition to both biosimilars launching at WAC and ASP discounts to the reference product, Zirabev—the second Avastin biosimilar—launched at a discount to the first biosimilar, MVASI.

**Figure 11. WAC and ASP of Bevacizumab Biosimilars Relative to Reference Product at Launch**

<table>
<thead>
<tr>
<th></th>
<th>MVASI launch (Jul 2019)</th>
<th>Zirabev launch (Jan 2020)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WAC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avastin</td>
<td>$797</td>
<td>$797</td>
</tr>
<tr>
<td>MVASI</td>
<td>$677</td>
<td>$677</td>
</tr>
<tr>
<td><strong>% Discount</strong></td>
<td>-15%</td>
<td>-15%</td>
</tr>
<tr>
<td>Avastin</td>
<td>$767</td>
<td>$677</td>
</tr>
<tr>
<td>MVASI*</td>
<td>$677</td>
<td>$677</td>
</tr>
<tr>
<td><strong>% Discount</strong></td>
<td>-12%</td>
<td>-11%</td>
</tr>
<tr>
<td>Zirabev</td>
<td>$613</td>
<td>$613</td>
</tr>
<tr>
<td><strong>% Discount</strong></td>
<td>-23%</td>
<td>-19%</td>
</tr>
</tbody>
</table>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avastin</td>
<td>$767</td>
<td>$761</td>
</tr>
<tr>
<td>MVASI*</td>
<td>$677</td>
<td>$677</td>
</tr>
<tr>
<td><strong>% Discount</strong></td>
<td>-11%</td>
<td>-19%</td>
</tr>
<tr>
<td>Zirabev*</td>
<td>$613</td>
<td>$613</td>
</tr>
</tbody>
</table>

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

*ASP not available for these products at time of comparison. WAC price is used to compare with reference product ASP.

Source: Analysource.
Figure 12 shows the percentage change in the price of biosimilars over time when compared to the reference product’s ASP at the time that the first Avastin biosimilar was launched.

Figure 12. ASP of Bevacizumab Products at Biosimilars' Launches

Key: ASP – average sales price.
*Q2’20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar.
Biosimilar WAC price used for comparing against reference product ASP until biosimilar ASP is available.
Source: Analysource.
As seen in Figure 13, there has been a strong adoption of bevacizumab biosimilars, with MVASI capturing 38% share within 9 months.

Figure 13. Biosimilar Uptake Curve for Bevacizumab Products

*Q2'20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar. Source: OBU Customer Data Pack Weekly (IQVIA DDD + Chargeback).
Two rituximab biosimilars have launched—one in 2019 and the other in 2020—to compete with the reference product Rituxan:

**Launched at a Price\(^27\)**

- **Truxima** (rituximab-abbs): injection for intravenous use
  - 10% less than Rituxan’s WAC
  - 5% less than Rituxan’s ASP

- **Ruxience™** (rituximab-pvvr)
  - 24% less than Rituxan’s WAC
  - 20% less than Rituxan’s ASP
As Figure 14 shows, in addition to both biosimilars launching at WAC and ASP discounts to the reference product, Ruxience—the second Rituxan biosimilar—launched at a discount to the first biosimilar, Truxima.

**Figure 14. WAC and ASP of Rituximab Biosimilars Relative to Reference Product at Launch**

<table>
<thead>
<tr>
<th></th>
<th>Q4’19</th>
<th>Q1’20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WAC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituxan</td>
<td>$940</td>
<td>$940</td>
</tr>
<tr>
<td>Truxima</td>
<td>$846</td>
<td>$846</td>
</tr>
<tr>
<td>Ruxience</td>
<td>$717</td>
<td>$717</td>
</tr>
</tbody>
</table>

**ASP Comparison**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituxan</td>
<td>$893</td>
<td>$893</td>
</tr>
<tr>
<td>Truxima*</td>
<td>$846</td>
<td>$846</td>
</tr>
<tr>
<td>Ruxience*</td>
<td>$717</td>
<td>$717</td>
</tr>
</tbody>
</table>

*ASP not available for these products at time of comparison. WAC price is used to compare with reference product ASP. Source: Analysource.*
Figure 15 shows the percentage change in the price of biosimilars over time when compared to the reference product’s ASP at the time that the first rituximab biosimilar launched. Biosimilar competition to Rituxan is relatively new, and we have not yet seen price concessions.

Figure 15. ASP of Rituximab Products at Biosimilars’ Launches

Key: ASP – average sales price.

*Q2'20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar.
Biosimilar WAC price used for comparing against reference product ASP until biosimilar ASP is available.
Source: Analysource.
As seen in Figure 16, there has been limited adoption of rituxumab biosimilars so far. Truxima captured 17% share within the first couple of quarters, and Ruxience captured 3% within its first months of launch. With competition to Rituxan still relatively new, it remains to be seen if there will be a different trajectory in the future.

Figure 16. Biosimilar Uptake Curve for Rituximab Products

*Q2'20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar.
The biosimilars available for oncology supportive care consist of pegfilgrastim, filgrastim, and epoetin alfa. For each, we discuss:

1. **WAC and ASP of the biosimilar at launch compared to the reference product**
2. **ASP for the reference product and biosimilars since launch**
3. **Biosimilar uptake**

Oncology supportive care is the most mature US biosimilar category. The FDA approved GRANIX in 2012, though not under the pathway created by the BPCIA. ZARXIO was the first biosimilar approved under the 351(k) pathway (in 2015), and also the first biosimilar to become commercially available (also in 2015). As such, the category provides insights into how biosimilars and their reference products change over time, as well as how biosimilars may gain share over a period of 5 years.
Three pegfilgrastim biosimilars have launched since 2018 to compete with the reference product Neulasta (pegfilgrastim):

**Launched at a Price**

- **Fulphila**
  - (pegfilgrastim-jmdb) injection
  - **33%** less than Neulasta's WAC
  - **6%** less than Neulasta's ASP

- **Udenyca**
  - (pegfilgrastim-cbqv)
  - **33%** less than Neulasta's WAC
  - **5%** less than Neulasta's ASP

- **Ziextenzo**
  - (pegfilgrastim-bmez)
  - **37%** less than Neulasta's WAC
  - **6%** less than Neulasta's ASP

See Neulasta [Full Prescribing Information](#) for complete risk information.
ONCOLOGY SUPPORTIVE CARE

**Pegfilgrastim**

As Figure 17 shows, all 3 biosimilars launched at WAC and ASP discounts to the reference product. The second biosimilar (UDENYCA) launched roughly on par with the first biosimilar, Fulphila. The third biosimilar (ZIEXTENZO) launched with a WAC that was 37% less than the reference product’s WAC and at a discount to the first 2 biosimilars. However, UDENYCA and ZIEXTENZO both launched at a premium to the ASP of Fulphila.

*Figure 17. WAC and ASP of Pegfilgrastim Biosimilars Relative to Reference Product at Launch*

See Neulasta Full Prescribing Information for complete risk information.

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

*ASP not available for these products at time of comparison. WAC price is used to compare with reference product ASP.

Source: Analysource.
Pegfilgrastim

Figure 18 shows the percentage change in the price of biosimilars over time when compared to the reference product's ASP at the time that the first pegfilgrastim biosimilar launched. ASPs for Neulasta, Fulphila, and UDENYCA have continued to decline over time.

Figure 18. ASP of Pegfilgrastim Products at Biosimilars’ Launches

See Neulasta Full Prescribing Information for complete risk information.

Key: ASP – average sales price.

*Q2’20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar.

Biosimilar WAC price used for comparing against reference product ASP until biosimilar ASP is available.

Source: Analysource.
As seen in Figure 19, biosimilars now account for nearly 30% of sales by volume. However, pegfilgrastim biosimilars show a different uptake pattern than other biosimilars, where the first biosimilar to launch captured the most share. By comparison, the leading pegfilgrastim biosimilar by share is UDENYCA (21% share), which was the second pegfilgrastim biosimilar to launch. Fulphila, the first pegfilgrastim biosimilar to launch, has a 6% share. The newest pegfilgrastim biosimilar, ZIEXTENZO, has gained 1% share after launching in late 2019.

Figure 19. Biosimilar Uptake Curve for Pegfilgrastim Products

See Neulasta Full Prescribing Information for complete risk information.

*Q2'20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar. Source: OBU Customer Data Pack Weekly (IQVIA DDD + Chargeback).
Two filgrastim biosimilars have been approved and launched since 2015 along with GRANIX in 2013 to compete with the reference product NEUPOGEN (filgrastim):

- **Granix** (TBO-Filgrastim) Injection
  - Launched at a Price
  - 23% less than NEUPOGEN's WAC
  - 12% less than NEUPOGEN's ASP

- **Zarxio** (filgrastim-sndz)
  - Subcutaneous or Intravenous Injection 300 mcg/0.5 mL | 480 mcg/0.8 mL
  - 15% less than NEUPOGEN's WAC
  - 3% less than NEUPOGEN's ASP

- **Nivestym** filgrastim-aafi
  - 34% less than NEUPOGEN's WAC
  - 24% less than NEUPOGEN's ASP

**NOTE:** GRANIX is not a biosimilar. It was approved under a full Biologics License Application, which was submitted to the FDA before enactment of the biosimilar approval pathway.

See NEUPOGEN Full Prescribing Information for complete risk information.
As Figure 20 shows, in addition to both biosimilars and GRANIX‡ launching at WAC and ASP discounts to the reference product, Nivestym launched at a discounted WAC to its predecessor ZARXIO.

Figure 20. WAC and ASP of GRANIX and Filgrastim Biosimilars Relative to Reference Product at Launch

See NEUPOGEN Full Prescribing Information for complete risk information.

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

*ASP not available for these products at time of comparison. WAC price is used to compare with reference product ASP.

‡GRANIX is not a biosimilar. It was approved under a full Biologics License Application, which was submitted to the FDA before enactment of the biosimilar approval pathway.

Source: Analysource.
ONCOLOGY SUPPORTIVE CARE

Filgrastim

Figure 21 shows the percentage change in price over time when compared to NEUPOGEN’s ASP at the time GRANIX launched. By Q1 2020, both filgrastim biosimilars saw significant decreases in their ASPs, while the ASP for NEUPOGEN has remained relatively stable.

Figure 21. ASP of Filgrastim Products at Biosimilars’ Launches

See NEUPOGEN Full Prescribing Information for complete risk information.

Key: ASP – average sales price.
*Q2’20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar.
†NEUPOGEN®’s biosimilar price-response strategy focused on account-level provider contracting. This targeted approach modestly increased the ASP-eligible discount rate, resulting in a more stable ASP trend.
‡GRANIX is not a biosimilar. It was approved under a full Biologics License Application, which was submitted to the FDA before enactment of the biosimilar approval pathway.
Biosimilar WAC price used for comparing against reference product ASP until biosimilar ASP is available.
Source: Analysource.
As seen in Figure 22, the reference product has dropped to a 28% share, while ZARXIO has climbed to a 48% share.

**Figure 22. Uptake Curve for Filgrastim Products**

See NEUPOGEN Full Prescribing Information for complete risk information.

*Q2'20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar.
†GRANIX is not a biosimilar. It was approved under a full Biologics License Application, which was submitted to the FDA before enactment of the biosimilar approval pathway.
TRENDS

ONCOLOGY THERAPEUTICS
ONCOLOGY SUPPORTIVE CARE
NEPHROLOGY/ONCOLOGY SUPPORTIVE CARE
INFLAMMATION
One epoetin alfa biosimilar has launched since 2018 to compete with the reference products EPOGEN and PROCRIT (epoetin alfa):

Launched at a Price\textsuperscript{27}

\begin{itemize}
  \item 33\% less than EPOGEN's WAC
  \item 57\% less than PROCRIT's WAC
  \item 5\% less than EPOGEN's ASP
  \item 5\% less than PROCRIT's ASP
\end{itemize}

\textbf{NOTE:} EPOGEN and PROCRIT are the same molecule; however, they are marketed by 2 different companies in separate therapeutic areas. In addition, they have independent WACs but the same ASP.

Please \href{http://www.example.com}{click here} for Boxed Warning information for EPOGEN. See \href{http://www.example.com}{Full Prescribing Information} for complete risk information.
Epoetin Alfa

As Figure 23 shows, Retacrit launched at WAC and ASP discounts to the reference products EPOGEN and PROCRIT.

**Figure 23. WAC and ASP of Epoetin Alfa Biosimilars Relative to Reference Products at Launch**

<table>
<thead>
<tr>
<th></th>
<th>WAC</th>
<th>ASP</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPOGEN</td>
<td>$17</td>
<td>$12</td>
</tr>
<tr>
<td>Retacrit</td>
<td>$11</td>
<td>$11</td>
</tr>
<tr>
<td>PROCRIT</td>
<td>$26</td>
<td>$12</td>
</tr>
<tr>
<td>Retacrit</td>
<td>$11</td>
<td>$11</td>
</tr>
</tbody>
</table>

WAC Comparison

ASP Comparison

Please [click here](#) for Boxed Warning information for EPOGEN.

See [Full Prescribing Information](#) for complete risk information.

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

*ASP not available for these products at time of comparison. WAC price is used to compare with reference product ASP.

Source: Analysource.
Figure 24 shows the percentage change in the price of the biosimilar over time when compared to the reference products’ ASP at the time that the first epoetin alfa biosimilar launched. By Q2 2020, Retacrit’s ASP had declined dramatically since its ASP was established in April 2019. The ASP of the reference products EPOGEN and PROCRIT has steadily trended downward following Retacrit’s launch.

Figure 24. ASP of Epoetin Alfa Products at Biosimilars’ Launch27

Please click here for Boxed Warning information for EPOGEN. See Full Prescribing Information for complete risk information.

Key: ASP – average sales price.
*Q2’20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar.
Biosimilar WAC price used for comparing against reference product ASP until biosimilar ASP is available.
Source: Analysource.
Epoetin Alfa

As seen in Figure 25, Retacrit captured 25% share within 18 months of launch, while EPOGEN’s share has remained relatively stable around 60%.

Figure 25. Biosimilar Uptake Curve for Epoetin Alfa Products

*Q2’20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar. Source: OBU Customer Data Pack Weekly (IQVIA DDD + Chargeback).

Please click here for Boxed Warning information for EPOGEN.
See Full Prescribing Information for complete risk information.
For inflammation, we look at infliximab. We discuss:

1. **WAC and ASP of the biosimilar at launch compared to the reference product**

2. **ASP for the reference product and biosimilars since launch**

3. **Biosimilar uptake**

Three of the top 6 best-selling biologics are anti-inflammatories—REMICADE is the third best-selling anti-inflammatory—which may lead to significant cost-saving opportunities for biosimilars in this class.\(^{32}\)

AVSOLA, an infliximab biosimilar, was FDA approved in December 2019 and became commercially available in July 2020.\(^{3,6}\)
Three infliximab biosimilars have launched—in 2016, 2017, and 2020—to compete with the reference product REMICADE (infliximab):

**Launched at a Price²⁷**

- **Inflectra®** (infliximab-dyyb)
  - less than REMICADE’s WAC
  - more than REMICADE’s ASP
  - 15% 21%

- **RENFLIXIS** (infliximab-abda)
  - less than REMICADE’s WAC
  - less than REMICADE’s ASP
  - 35% 7%

- **AVSOLA™** (infliximab-axxq)
  - less than REMICADE’s WAC
  - more than REMICADE’s ASP
  - 57% 4%

Please [click here](#) for Boxed Warning information for AVSOLA.
See [Full Prescribing Information](#) for complete risk information.
TRENDS: INFLAMMATION

Infliximab

As Figure 26 shows, all infliximab biosimilars launched at WAC discounts to the reference product. Virtually all biosimilars in the US have also launched with discounts to the reference product’s ASP; however, Inflectra and AVSOLA launched at a premium to the reference product REMICADE’s ASP. The second biosimilar, RENFLEXIS, also launched at a WAC discount to the first biosimilar, Inflectra, and provided WAC and ASP discounts compared with the reference product.

Figure 26. WAC and ASP of Infliximab Biosimilars Relative to Reference Product at Launch27

<table>
<thead>
<tr>
<th></th>
<th>Q4'16</th>
<th>Q3'17</th>
<th>Q3'20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WAC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REMICADE</td>
<td>$1,113</td>
<td>$1,168</td>
<td>$1,168</td>
</tr>
<tr>
<td>Inflectra</td>
<td>$946</td>
<td>$946</td>
<td>$946</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td>-15%</td>
<td>-19%</td>
<td>-19%</td>
</tr>
<tr>
<td><strong>ASP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REMICADE</td>
<td>$782</td>
<td>$809</td>
<td>$483</td>
</tr>
<tr>
<td>Inflectra</td>
<td>$946</td>
<td>$753</td>
<td>$471</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td>+21%</td>
<td>-7%</td>
<td>-2%</td>
</tr>
</tbody>
</table>

REMICADE Inflectra RENFLEXIS AVSOLA

<table>
<thead>
<tr>
<th></th>
<th>Q3'17</th>
<th>Q3'20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WAC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REMICADE</td>
<td>$1,168</td>
<td>$1,168</td>
</tr>
<tr>
<td>Inflectra</td>
<td>$946</td>
<td>$946</td>
</tr>
<tr>
<td>RENFLEXIS</td>
<td>$753</td>
<td>$753</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td>-35%</td>
<td>-35%</td>
</tr>
<tr>
<td><strong>ASP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REMICADE</td>
<td>$483</td>
<td>$483</td>
</tr>
<tr>
<td>Inflectra</td>
<td>$471</td>
<td>$471</td>
</tr>
<tr>
<td>RENFLEXIS</td>
<td>$486</td>
<td>$486</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td>+4%</td>
<td>+4%</td>
</tr>
</tbody>
</table>

REMICADE Inflectra* RENFLEXIS* AVSOLA*

*ASP not available for these products at time of comparison. WAC price is used to compare with reference product ASP.

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

Please click here for Boxed Warning information for AVSOLA.

See Full Prescribing Information for complete risk information.

Source: Analysource.
Figure 27 shows the percentage change in the price of biosimilars over time when compared to the reference product’s ASP at the time that the first infliximab biosimilar launched. Despite launching at a premium to the reference product’s ASP, Inflectra’s price quickly moved below REMICADE’s ASP 3 quarters later once its ASP was established. The ASPs for REMICADE, Inflectra, and RENFLEXIS continued to decrease almost every quarter after the launch of the second infliximab biosimilar, RENFLEXIS.

Figure 27. ASP of Infliximab Products at Biosimilars’ Launches

Key: ASP – average sales price.

*Q2’20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar. With a launch date of July 6, 2020, AVSOLA™ data are unavailable at time of comparison and excluded from figure. Biosimilar WAC price used for comparing against reference product ASP until biosimilar ASP is available. Source: Analysource.

Please click here for Boxed Warning information for AVSOLA. See Full Prescribing Information for complete risk information.
As seen in Figure 28, biosimilars are beginning to capture a greater proportion of share compared to the reference product. After slow starts, Inflectra and RENFLEXIS had each gained 10% share by early 2020, while the reference product REMICADE has an 80% share.

**Figure 28. Biosimilar Uptake Curve for Infliximab Products**

Please click here for Boxed Warning information for AVSOLA. See Full Prescribing Information for complete risk information.

*Q2’20 sales data through July 3, 2020; monthly rollup based on 4-4-5 calendar. With a launch date of July 6, 2020, AVSOLA™ data are unavailable at time of comparison and excluded from figure. Source: OBU Customer Data Pack Weekly (IQVIA DDD + Chargeback).*
KEY CONSIDERATIONS

Providers

Healthcare professionals, including physicians, physician assistants, nurse practitioners, and pharmacists, are central to the adoption of biosimilars. Healthcare professionals must have confidence in the evidence and the approval process, and physicians specifically must have the confidence to prescribe and use biosimilars.

Providers should ensure that their practices have operational processes in place to prepare for use of biosimilars. Also, practices and institutions such as hospitals will need assurance that biosimilars are covered by payers and are reimbursed in a timely fashion.

Finally, physicians have a central role in educating patients and ensuring biosimilars can be safely used in everyday clinical practice.

Educational campaigns

Science-based education about these products will provide stakeholders with greater confidence in their use. 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.33,34

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 on educating their members about biosimilars.35,36

CANCER: In 2018, ASCO published a policy statement in its clinical journal and on its website to help increase the understanding of biosimilars among the cancer care community.37

RARE DISEASES: In 2019, the rare-disease patient and provider community issued a set of common principles to promote the use of biosimilars.38
Providers

Five years after the first biosimilar launched in the US, physician knowledge of biosimilars in each specialty where they are available continues to grow.

However, there is work to be done. A 2018 survey of 442 clinicians, conducted by the Health Research Institute of PricewaterhouseCoopers (PwC), found that 55% of clinicians were unfamiliar with biosimilars. The study also indicated that 35% of physicians said they have never prescribed a biosimilar. A total of 65% of respondents indicated they would be more willing to prescribe biosimilars if there was a meaningful cost difference for their patients.

Surveys conducted in 2018 show that specialists who have frequently prescribed biologics in the past (eg, oncologists and hematologists) are knowledgeable about biosimilars and are confident about prescribing them to their patients.

“Biosimilar medicines are established among many physicians, but some uncertainty regarding the regulatory pathway and efficacy remains—not only for those in cancer centers, but for all healthcare facilities. In the supportive care space, use of biosimilar medicines is greater because of higher comfort with their use for these applications vs medical interventions, where the outcomes of cancer treatment are the tangible endpoint.”

– Lee S. Schwartzberg, MD, Executive Director, West Cancer Center

Why have a sales force?

It is important for manufacturers to support their biosimilar products with a capable sales force. There are still knowledge gaps related to biosimilars among all participants in the healthcare system, including patients, payers, pharmacists, and healthcare professionals. A well-prepared sales force can help address those knowledge gaps.
Oncologists appear to be more familiar with biosimilars than other specialties. In a primary market research study published in 2018, as described in Table 1, 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. 33

**Table 1. US Community Oncologists’ and Hematologists’ Familiarity With Biosimilars**

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

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

Clearly, continuing education is necessary to increase physician understanding and prescribing of biosimilars. A 2019 survey of 100 doctors conducted by AmerisourceBergen found that, even though physicians ranked their confidence in their ability to use biosimilars generally high, they paradoxically ranked their own confidence as the top barrier to biosimilar adoption, as shown in Figure 29. 40

**Figure 29. Barriers to Biosimilar Adoption**

What do you see as the biggest barriers to widespread adoption of biosimilars?

- Physician confidence: 74%
- Payers: 58%
- Patient education: 30%
- Health policy: 27%
- Litigation: 19%
- Other: 2%
Providers

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 potential differences in delivery device between a reference product and a biosimilar
- Understanding differences in electronic health record tracking when stocking the reference product and biosimilar
- 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 Good Manufacturing Practice standards. Biosimilar manufacturers must have a long-term commitment to quality for biosimilars 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.
KEY CONSIDERATIONS

PROVIDERS

PAYERS AND EMPLOYERS

PATIENTS

BENEFITS AND CONSIDERATIONS
KEY CONSIDERATIONS

Payers and Employers

Payers
Payers are looking to biosimilars as an opportunity to help control costs and offer more treatment choices. The availability of biosimilars in key therapeutic categories that currently have only 1 or a few originator biologics available promotes competition and is a tool payers and other stakeholders can use to help lower costs.

Payers must evaluate several clinical and economic factors when considering adding biosimilars to formulary, including:

- Existing clinical trial and post-marketing evidence
- How biosimilars will be covered and placed on formularies
- Utilization management mechanisms
- Cost-effectiveness
- Whether physicians will be willing to prescribe them
- Whether, how, and when to switch patients to biosimilars
- Their potential to decrease costs while maintaining patient access to necessary treatments
**KEY CONSIDERATIONS**

**Payers and Employers**

**Payer adoption of biosimilars**

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

For example, effective October 1, 2019, UnitedHealthcare required its commercial and Medicare Advantage customers to use KANJINTI and MVASI before the reference products Herceptin (trastuzumab) and Avastin (bevacizumab), respectively.\(^{43}\)

Pharmacy benefit managers (PBMs) also benefit from the cost-savings of biosimilars. Prime Therapeutics recommended 3 of its Blue Cross Blue Shield (BCBS) clients change their medical policies to prefer biosimilars over the reference product for granulocyte-colony stimulating factor drugs, starting in the first half of 2019.\(^ {44}\) Meanwhile, other BCBS clients of Prime Therapeutics added biosimilars to their formularies but did not prefer the reference product or biosimilars.

By year-end 2019, the formulary-neutral BCBS plans saw biosimilar conversions at about 18%, while the the 3 BCBS plans that had an active management approach preferring biosimilars saw high conversion rates of 70%, 73%, and 97%. Collectively, this delivered a cost savings of $4 million.\(^ {44}\)

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Please [click here](#) for Boxed Warning information for KANJINTI.
KEY CONSIDERATIONS

Payers and Employers

Payer adoption of biosimilars

In 2019, CVS Caremark made several formulary changes to categories that included biosimilars. The PBM acknowledged that its approach to maximizing the savings potential of biosimilars is using competition to help drive the lowest net cost for its payer customers. It indicated biosimilars can lower costs in 2 ways:

- By encouraging uptake of the biosimilars as the lower-cost alternative
- OR
- By contributing to competition that results in a lower price of the reference product

Biosimilars offer the potential of cost savings through 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 to promote formulary access as well.
Payers and Employers

Employers

With over 157.3 million people (49% of the US population) covered by employer-sponsored insurance, employers have a vested interest in controlling and containing healthcare costs.\(^46\) Biosimilars are a potential path forward to reduce costs for 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 budget line item for employers over the last 10 years. Large companies estimate that their total cost of healthcare, including premiums and out-of-pocket costs for employees and dependents, will increase 6% to $15,375 per employee in 2020, up from $14,642 per employee in 2019.\(^47\)

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.\(^48\) The estimates were slightly lower for 2020: Mercer estimated a 3.9% increase, while PwC’s Health Research Institute projected a 6% increase.\(^49,50\)

Nevertheless, both projections of the increase in healthcare costs exceed expectations for inflation.

Biosimilars work best in a competitive environment. Payers are excited about the wave of biosimilars becoming available, 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.
KEY CONSIDERATIONS

Payers and Employers

Biosimilar adoption and impact for employers

Escalating specialty drug costs present a challenge for many employers trying to control their healthcare spend while maintaining a profitable business. Continued biosimilar penetration could help increase competition and lower costs without compromising quality, efficacy, or patient safety. One strategy that is advocated to lower employers’ cost burden is the integration of value-based policies to help navigate the challenges of rebates, provider incentives, and provider education of biosimilars.51

A 2018 case study by the Pacific Research Institute found that if biosimilars can reach 50% share 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 markup percentage.52

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”54:

- 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

The 24th annual Best Practices in Health Care Employer Survey by Willis Towers Watson found 30% of employers have created incentives and requirements to promote the use of biosimilars in their formulary or plan design, and another 39% of employers plan to explore this strategy in the next 2 years.53

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”54:
KEY CONSIDERATIONS

PROVIDERS

PAYERS AND EMPLOYERS

PATIENTS

BENEFITS AND CONSIDERATIONS
Patients

Patient understanding of biosimilar products, including their safety and efficacy, will be key to the utilization of these drugs. Education on what biosimilars are and the potential for cost savings will be of paramount importance to encourage their utilization.

Patients should understand the following points:

- What is a biosimilar? Is it safe and effective?\(^{55,56}\)
- Do biosimilars undergo the same clinical trial process as other FDA-approved products? If not, is that okay?\(^{56}\)
- How much will a biosimilar cost me, and is it a cheaper product? Are there patient assistance programs for biosimilars to help me with these costs?
- If there is an FDA-approved biosimilar for the biologic I’m taking, is it worth me switching to it?\(^{10}\)
KEY CONSIDERATIONS

- PROVIDERS
- PAYERS AND EMPLOYERS
- PATIENTS
- BENEFITS AND CONSIDERATIONS

EXECUTIVE SUMMARY
CURRENT STATE OF THE MARKETPLACE
TRENDS
KEY CONSIDERATIONS
REIMBURSEMENT
POLICY CONSIDERATIONS
BIOSIMILARS IN REVIEW
REFERENCES
Benefits and Considerations

Benefits to society, payers, providers, and patients

Biosimilars offer potential benefits to every stakeholder in the healthcare system. They can lower spending by offering a potentially lower-cost treatment option. 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. 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.58,59 As a result, manufacturers have fewer expenses to recoup, which theoretically contributes to the possibility of biosimilars having 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 remain competitive.

Things to think about

Biosimilars have the potential to benefit the healthcare system. Biosimilars’ lower prices can contribute to reduced costs—and their introduction contributes to competition, including potentially lower prices of reference products. Additionally, these savings can be used to expand treatment options for patients.
REIMBURSEMENT
Medicare Updates

Several reimbursement developments affecting biosimilars occurred in the last 12-15 months that are worth noting.

As of January 2018, the Centers for Medicare and Medicaid Services (CMS) has assigned each biosimilar a unique Healthcare Common Procedure Coding System (HCPCS) code, and its ASP will not be combined with those of other biosimilars. This is a positive change from previous billing and coding policy that grouped biosimilars with a common reference product in the same HCPCS code.

Assigning a unique HCPCS code to each biosimilar can help promote a robust, competitive landscape by:

- Increasing the potential for innovation
- Lowering risks associated with developing and marketing these complex products
- Helping to level the playing field for reference products and biosimilars by reducing some of the concerns and confusion for traceability created by shared HCPCS codes

Biosimilars and reference products now operate on a level playing field in terms of coding.

Please refer to the Biosimilars in Review section at the end of the report for coding, coverage, and payment characteristics of biosimilars among various payers.
Medicare Updates

The Affordable Care Act (ACA) included language to promote a level playing field between reference products and biosimilars. As shown in Figure 30, Medicare Part B reimburses physicians for biosimilars at the biosimilar’s ASP plus a 6% add-on (4.3% after sequestration) of the reference biologic’s ASP. 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 helps all manufacturers to compete on equal terms.

**Figure 30. Medicare Part B Reimbursement for Biosimilars**

Key: ASP – average sales price.
Because there is often a lag time of 2 calendar quarters from the time when a product launches until its ASP is published, as of January 2019, Medicare reimburses Part B drugs—including biosimilars—based on their WAC plus a 3% add-on until the ASP becomes available. Once ASP data are available, Medicare reimburses biosimilars using the ASP methodology (ASP plus 6% of the reference product’s ASP). 61,62

**IMPORTANT:** In April 2020, the Coronavirus Aid, Relief, and Economic Security (CARES) Act was signed into law. One of its provisions suspended the sequester, including the 2% mandatory payment reduction for the Medicare program, from May 1, 2020, to December 31, 2020. 63

Table 2 shows hypothetical examples of physician office or community clinic and outpatient payments for a biosimilar under Medicare Part B. 62

**Table 2. Payment Methodology for Biosimilars Under Medicare Part B** 61,62

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

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

*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%.
REIMBURSEMENT

340B Program

The 340B Drug Pricing 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. Sites within a healthcare system that qualify as 340B entities can obtain federally mandated “ceiling price” discounts for covered outpatient drugs.64

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.65 Effective January 1, 2018, however, Medicare pays for non-pass-through drugs and biologics (other than vaccines) purchased through the 340B program at ASP minus 22.5%.66 (This reduced payment methodology is now in question, due to a lawsuit brought by the American Hospital Association and others, as discussed in the “Ongoing Story” callout.)

<table>
<thead>
<tr>
<th>Ongoing Story</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 2018 and 2019, CMS instituted a nearly 30% payment reduction to 340B drugs by changing their reimbursement rate from ASP plus 6% to ASP minus 22.5%. A court decision in December 2018 ruled CMS did not have the authority to change the payment rate and, to minimize the impact to federal spending, the court ordered CMS to collect more information to present before a ruling could be made.68</td>
</tr>
<tr>
<td>In February 2020, CMS published a notice in the Federal Register announcing its intent to survey hospitals and acquire the payment rates for drugs purchased under the 340B program.69 CMS stated it would plan to use the information collected on acquisition cost to determine future payment rates for these drugs under the program. The proposed survey request is the response from CMS to the ongoing litigation involving drugs purchased under the 340B discount program and their reimbursement rates.</td>
</tr>
</tbody>
</table>
REIMBURSEMENT

340B Program

For non-pass-through biosimilars purchased through the 340B program, CMS will continue its policy of paying ASP minus 22.5% of the biosimilar’s ASP.\(^{70}\)

For calendar year 2020, CMS continues its current policy to make all biosimilars eligible for pass-through payment, not just the first biosimilar for a reference product.\(^{71}\) Additionally, CMS continued its 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%).\(^{72}\) The box below describes Medicare reimbursement for biosimilars under the 340B program.

Medicare reimbursement for biosimilars under the 340B program\(^{72}\)

<table>
<thead>
<tr>
<th>All biosimilars with pass-through payment status (not just the first biosimilar for a reference product)</th>
<th>= ASP + 6% of Reference Biologic’s ASP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosimilars without pass-through payment status</td>
<td>= ASP - 22.5% of Biosimilar’s ASP (not the reference product’s ASP)</td>
</tr>
</tbody>
</table>

Key: ASP – average sales price.
REIMBURSEMENT

340B Program

Table 3 shows an example of a comparison of reference biologic and biosimilar Part B reimbursement in the hospital outpatient department. The Medicare payment amounts for products under the 340B 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.

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 program.

Table 3. Hospital Outpatient Department Payment Methodology for 340B Reference Biologics and 340B Biosimilars in Medicare Part B

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WAC (List Price)</td>
<td>$1,000.00</td>
<td>$800.00</td>
<td>$800.00</td>
</tr>
<tr>
<td>ASP</td>
<td>$800.00</td>
<td>$640.00</td>
<td>$640.00</td>
</tr>
<tr>
<td>6% of Reference Product’s ASP</td>
<td>N/A</td>
<td>$48.00</td>
<td>N/A</td>
</tr>
<tr>
<td>22.5% of its Own ASP</td>
<td>$180.00</td>
<td>N/A</td>
<td>$144.00</td>
</tr>
<tr>
<td>Hospital Outpatient Payment Rate</td>
<td>$620.00</td>
<td>$688.00</td>
<td>$496.00</td>
</tr>
<tr>
<td>(before sequestration)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital Outpatient Payment Rate</td>
<td>$610.08</td>
<td>$676.99</td>
<td>$488.06</td>
</tr>
<tr>
<td>(after sequestration)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Cost-Share (20%)</td>
<td>$124.00</td>
<td>$137.60</td>
<td>$99.20</td>
</tr>
</tbody>
</table>

Key: ASP – average sales price; N/A – not applicable; WAC – wholesale acquisition cost.

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

New product entrants will always face considerable challenges. For example, reference products have greater familiarity and longer clinical background. Recent legislative and regulatory actions have attempted to level the playing field, although some proposals have been designed to be preferential to biosimilars.

For example, the now-stalled 2019 Senate Bill the Prescription Drug Pricing Reduction Act includes a policy change that would allow providers to get a higher reimbursement rate for biosimilars than for the reference products. This development goes beyond fair competition and provides mechanisms to favor biosimilars.

Policies that place biosimilars on a level playing field with reference products will help create fair competition and allow innovation to drive the landscape. These policies will help create the foundation for rapid growth of biosimilars over the near future.

“I’m pleased to announce ... that we’re releasing our Biosimilars Action Plan...

Our aim is to reduce the time, uncertainty, and cost of drug development, while also supporting a competitive market through the efficient approval of lower-cost generic, biosimilar, and interchangeable alternatives after the expiration of patents or other statutory exclusivities.

This cycle of market-based innovation and competition has helped make America’s biopharmaceutical industry the leader among our global peers in Asia and Europe.”

– Scott Gottlieb, MD, FDA Commissioner
POLICY CONSIDERATIONS

In 2018, the FDA announced its Biosimilars Action Plan (BAP), further demonstrating its commitment to helping the US achieve and maintain a robust marketplace with biosimilars. The BAP’s central thesis is that competition can and should be leveraged to reduce drug prices. The BAP applies many lessons the FDA learned from its experience with generic drugs to accelerate biosimilar competition, distilled into the following key goals:

- 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 competitors by reducing gaming of FDA requirements or other attempts to unfairly delay competition

In 2019 and 2020 (to date), the US continued to foster a competitive marketplace for biologics with additional regulatory policies.

In May 2019, the FDA finalized long-awaited guidance spelling out how biosimilars can achieve an interchangeable status, which means they may be substituted for the reference biologic without a prescriber intervening, consistent with state laws.

So far, the FDA has not designated any biosimilar to be interchangeable to its reference product.

As of May 2019, only 2 manufacturers had publicly announced an effort to demonstrate interchangeability.
In February 2020, the FDA announced it would be upgrading the Purple Book, its database of FDA-licensed biological products. The anticipated updates, which will be rolled out in phases, have already begun. Features include:

- Type of BLA submitted
- Product presentation
- Dosage form and strength
- License status
- Full search functionality for both approved biosimilars and their reference products

The FDA commissioner stated how the Purple Book will benefit biosimilars:

“Providing stakeholders with more information about biological products through a modernized platform should better facilitate the acceptance and use of existing biosimilar products and the development of new ones, potentially leading to lower costs for patients and improved access to safe, effective, high-quality medications.”

– Stephen M. Hahn, MD, FDA Commissioner

Access the Purple Book [here](#).
Effective March 23, 2020, based on a provision of the BPCIA, approximately 100 products approved under New Drug Applications (NDAs) transitioned to be licensed under BLAs. Among the transitioned products were insulin and human growth hormone.

**Why is this important?**

A reference product must be approved in a BLA for biosimilar and interchangeable versions to reference it; products approved in a NDA are not eligible to serve as reference products.

Because of that statute, more biosimilars will be possible for biologics, such as insulin, and this should inject new competition into some prevalent therapeutic areas.

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

UNDERSTANDING BIOSIMILARS

FDA APPROVAL PATHWAY

EXTRAPOLATION, INTERCHANGEABILITY, SWITCHING, AND SUBSTITUTION

PHARMACOVIGILANCE AND NAMING
A biosimilar is a biologic that is highly similar to, and has no clinically meaningful differences from, another biologic that’s already approved by the FDA (known as the original biologic or reference product).82

Compared to small-molecule drugs, including generic medicines, biologics (which include biosimilars) are large-molecule drugs that are far more structurally complex.84

By contrast, generics are drugs that are chemically and therapeutically equivalent to the branded, originator small-molecule drugs.83

The pathway for FDA approval of biosimilars was specifically established by Congress to account for differences between biosimilars and generic drugs.
Understanding Biosimilars

**Figure 31. Comparison of Size and Complexity of Small-Molecule Drugs and Biologics**

- **Small-Molecule Drug**
  - Generics: Same structure as reference drug
  - Acetylsalicylic acid: 180 Da
  - Insulin: ~5,800 Da

- **Biologics**
  - Biosimilars: Highly similar structure to reference biologic
  - Growth hormone: ~22,100 Da
  - mAb: ~150,000 Da

**Key**
- Da – dalton, 1 atomic mass unit
- mAb – monoclonal antibody
**Figure 31. Comparison of Size and Complexity of Small-Molecule Drugs and Biologics**

<table>
<thead>
<tr>
<th>SMALL-MOLECULE DRUG</th>
<th>BIOLOGICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENERICS: Same structure as reference drug</td>
<td>BIOSIMILARS: Highly similar structure to reference biologic</td>
</tr>
</tbody>
</table>

**Key**: Da – dalton, 1 atomic mass unit; mAb – monoclonal antibody.
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.80

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.58

Due to the complex nature and production methods of biologics, relatively minor changes in manufacturing processes may significantly affect product quality, safety, and efficacy.10,89

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 following10,15:

- Identify any differences between the reference and biosimilar products.
- Determine what residual uncertainty about biosimilarity remains based on the potential impact of the observed difference.
- Design subsequent studies to address the remaining residual uncertainty.
As shown in Figure 32, while a biosimilar may require more analytical characterization and functional assessments than reference products, it may need fewer clinical trials and clinical pharmacology studies than its reference product to obtain FDA approval. Due to the ability to rely 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.

Figure 32. Reference Product Development vs Biosimilar Development

Reference Product Development
Demonstrate safety, purity, and potency

Biosimilar Development
Demonstrate biosimilarity to the reference product

Clinical Studies
(Safety, efficacy, immunogenicity)

Clinical Pharmacology
(PK/PD)

Nonclinical Studies

Analytical Characterization
(Structure and function assessment)

Key: PK/PD – pharmacokinetics/pharmacodynamics.
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.90

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.90

The goal of a biosimilar development program is not to independently establish the safety and efficacy of the biosimilar product, but to demonstrate that the proposed biologic product is biosimilar to the reference product. 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.
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, a manufacturer can “extrapolate” data and information supporting biosimilarity in one condition of use to other conditions of use for which the reference product is licensed, as shown in Figure 33.

**Figure 33. Extrapolation of Indications**

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.

The expectation for most biosimilar drugs is that they will be approved for the same indications as the reference product. However, a biosimilar may be approved with fewer indications than the reference product because of a manufacturer’s inability to provide adequate scientific justification to support extrapolation or due to intellectual property protections.
Figure 33. Extrapolation of Indications

**BIOSIMILAR DEVELOPMENT**

**PRIMARILY INDICATION**

National regulatory agencies’ previous finding of safety and efficacy for the reference product

- Extrapolated Indication
- Extrapolated Indication
- Extrapolated Indication

- Extrapolated Indication
- Extrapolated Indication

**SCIENTIFIC JUSTIFICATION**

- MECHANISM OF ACTION
- PHARMACOKINETICS
- IMMUNOGENICITY
- EFFICACY AND SAFETY
- TOXICITY

TOTALITY OF EVIDENCE

Studied Indication
A “biosimilarity” determination by the FDA is a necessary, but not sufficient finding to allow substitution at the pharmacy. Per US state pharmacy laws (49 states plus Puerto Rico have passed legislation), a biosimilar must also be designated by the FDA to be “interchangeable” with its reference product to be eligible for pharmacy substitution. The FDA designates a biosimilar as “interchangeable” if, in addition to demonstrating biosimilarity, 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.

An interchangeable biosimilar product 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.

In May 2019, the FDA released final guidance to assist manufacturers in demonstrating that a proposed therapeutic protein product is interchangeable with a reference product.75

For interchangeability, FDA guidance indicates that it is generally expected for a manufacturer to conduct 1 or more “switching studies” that will assess the safety or efficacy of alternating between the reference biologic drug product and the biosimilar.
BIOSIMILARS IN REVIEW

Extrapolation, Interchangeability, Switching, and Substitution

In the absence of the FDA or a state permitting the automatic substitution of biosimilars, hospitals, health plans, and pharmacy benefit managers may use other formulary management techniques including “therapeutic interchange” as a mechanism to substitute a biosimilar for its reference product.93

Therapeutic interchange is the process of reimbursing 1 product rather than another when both products are expected to produce similar clinical effects and outcomes based on scientific evidence.93
Pharmacovigilance and Naming

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

Generic drugs and their brand drugs share the same nonproprietary name because they are chemically identical. However, reference biologics and biosimilars are highly similar but not chemically identical. Distinguishable nonproprietary names facilitate pharmacovigilance and help avoid inappropriate substitution at the pharmacy level.

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.

The example in Table 4 shows the illustrative hypothetical nonproprietary names of a reference product and its biosimilar:

<table>
<thead>
<tr>
<th>Reference Product</th>
<th>Core Name</th>
<th>Distinguishing Suffix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference Product</td>
<td>Same Core Name</td>
<td>-agdb</td>
</tr>
<tr>
<td>Biosimilar</td>
<td>Same Core Name</td>
<td>-eyfp</td>
</tr>
</tbody>
</table>

The FDA’s goals, as stated in the final guidance on naming:

- Use distinguishable suffixes to facilitate pharmacovigilance and to prevent inadvertent substitution
- Help promote proper attribution of safety events and effective tracking of biosimilars
- Help to minimize risk that a noninterchangeable product is substituted in place of the prescribed reference product when interchangeable products become available

The benefits of the naming convention should bolster patient and physician confidence, and encourage manufacturer accountability by providing additional ways to help prescribed products be tracked appropriately.
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