

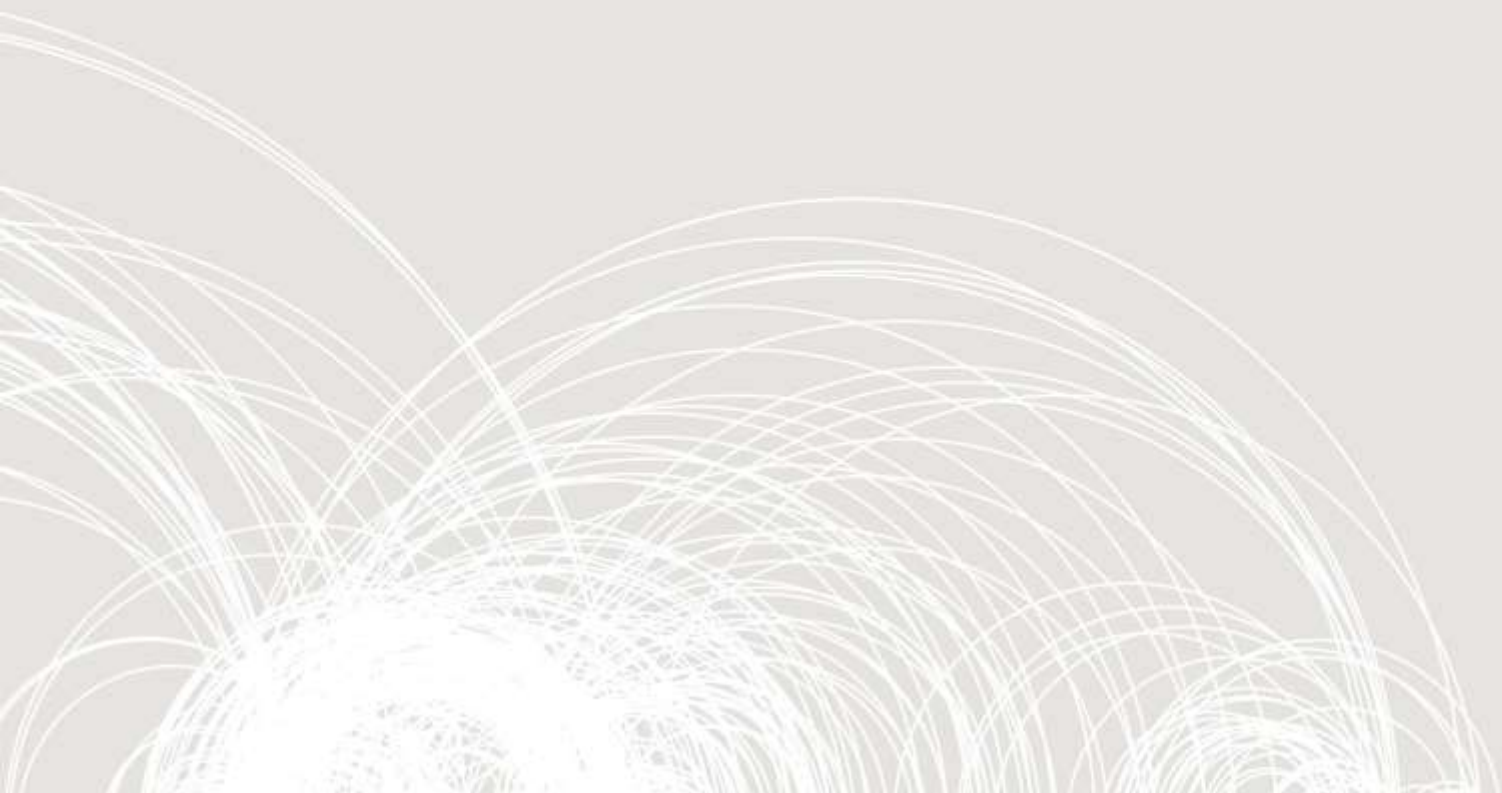
## **BIOSIMILAR PLAYBOOK**

September 2023

# **Supply Chain Incentives: Infliximab (Remicade / Unbranded Infliximab, Avsola, Inflectra, Renflexis)**

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## About This Series

This paper is organized to highlight each medication or therapy in this series three phases: production, commercialization, and access.

Within production, there are critical steps and decisions that manufacturers make regarding research and development, patenting, and manufacturing.

From there, commercialization is intended to look closely at how a product is marketed, labeled, and regulated, and the resultant impact of those decisions on the price of each featured product.

The final step in the process is access, how product acquisition (moving from manufacturer, through wholesalers, and on to pharmacies) and distribution (PBMs, payers, and providers) shapes patient access, which is so often impacted by cost.

## Introduction

Infliximab is a much-prescribed biologic product used to treat autoimmune conditions such as Crohn's disease and ulcerative colitis. The originator infliximab product approved in the U.S. was Remicade, which is still on the market today. Remicade was approved in 1998,<sup>1</sup> and until 2016, was the only approved version of infliximab. Since then, four infliximab biosimilars have been approved by the U.S. Food and Drug Administration (FDA) and three have come to market in the U.S. as of June 2023: Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), and Renflexis (infliximab-abda). Biologics, including infliximab, are often administered via injection or infusion and are typically given only under close supervision of a medical professional. As of August 2022, the FDA has licensed 621 biologics products<sup>2</sup> that treat a wide variety of conditions.<sup>3</sup>

Biosimilars are biologic drugs that are "highly similar" to existing biologic agents (often called the reference biologic) and have been determined to present no clinically meaningful differences from the reference in their efficacy or safety.<sup>4</sup> Though not a perfect analog of traditional "generics" to small-molecule drugs (e.g., pills), biosimilars are often thought of as "generic biologics." Since the passage of the Biologics Price Competition and Innovation Act (BPCIA) in 2010 as part of the Patient Protection and Affordable Care Act (ACA), the FDA has approved 40 biosimilars, with the first biosimilar approved in 2015. However, only 27 of the 40 are available to patients in the U.S. as of 2023.<sup>5</sup>

The biologics market in the U.S., inclusive of biosimilars, is the fastest growing pharmaceutical category, experiencing a compound annual growth rate of 12.5%.<sup>6</sup> Total U.S. spending on medicines was \$568 billion in 2021, and biologics and biosimilars represented nearly half of that with \$261 billion, or 46% of total spend. Today, 14% of the biologics market experiences biosimilars competition, and it is expected that 70% of the biologics market in the U.S. will face future biosimilars competition.<sup>7</sup>

Biosimilars, much like generics for small molecule drugs, offer great promise in increasing competition and lowering the price of reference biologics, which would result in lower per capita spending across all biologics in the U.S. However, that promise has yet to be fully realized. This playbook uses the real-world example of infliximab to describe the complex landscape of biologics, including the market incentives facing manufacturers of innovator products and biosimilar competitors, with a specific focus on products that are purchased by physicians and administered to patients in an office setting.

<sup>1</sup> FDA Purple Book. (2023). <https://purplebooksearch.fda.gov/results?query=infliximab&title=Remicade>

<sup>2</sup> Office of the Commissioner & Office of the Commissioner. (2022, August 17). *Fact Sheet: FDA at a Glance*. U.S. Food And Drug Administration. <https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance>

<sup>3</sup> E.g., cancer, psoriasis, rheumatoid arthritis (RA), inflammatory bowel diseases

<sup>4</sup> 42 U.S. Code § 262 - Regulation of biological products. (n.d.-b). LII / Legal Information Institute. [https://www.law.cornell.edu/uscode/text/42/262#:~:text=\(2\)%20The%20term%20%E2%80%9Cbiosimilar,in%20clinically%20inactive%20components%3B%20and](https://www.law.cornell.edu/uscode/text/42/262#:~:text=(2)%20The%20term%20%E2%80%9Cbiosimilar,in%20clinically%20inactive%20components%3B%20and)

<sup>5</sup> AmerisourceBergen. (2003). *U.S. Biosimilar Report*. <https://www.amerisourcebergen.com/-/media/assets/amerisourcebergen/biosimilars-page/sgs-biosimilars-usmarketlandscape-020623--copy.pdf>

<sup>6</sup> Biosimilars in the United States 2023–2027. (2023). In IQVIA. <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/biosimilars-in-the-united-states-2023-2027/iqvia-institute-biosimilars-in-the-united-states-2023-usl-orb3393.pdf>

<sup>7</sup> Ibid.

This playbook also shows that once biosimilars come on the market, they do have a flattening effect on the net prices of reference biologics. However, price alone is not the ultimate arbiter of access and many patients are still paying high prices for these products, which drives spend across the entire industry.

## Impact of Incentives

### Production

#### *Patenting*

A myriad of market dynamics like extensions on patent exclusivity, “patent thickening,” and the “patent dance” may make it more difficult for biosimilar entry and competition in the biologics market. Manufacturers of innovator, or reference, biologics approved by the FDA are given a 12-year exclusivity period—seven years longer than the patent exclusivity period granted to small molecule drugs. Biosimilar applications can be submitted as early as four years after approval of the reference product, but numerous barriers to entry and utilization exist for biosimilar manufacturers. Some reference, or originator, biologic manufacturers effectively extend their patents beyond the formally regulated exclusivity period by filing multiple patents based on minor variations on the primary patent. This practice is known as “patent thickening” and is not uncommon across the industry. On average, each of the top 10 selling drugs in U.S. are protected by more than seven patents each, underscoring the legal patent landscape facing would-be biosimilar competitors.<sup>8</sup> Janssen Pharmaceuticals, Inc. (Janssen), the manufacturer of Remicade, has filed applications seeking to extend the patent on Remicade to 2025, which would mean their patent protection effectively extends for 27 years.<sup>9</sup>

While “patent thickening” is a tactic utilized to extend regulatory exclusivity, reference biologic manufacturers also employ another legal practice known as the “patent dance” to delay entry of competitors.<sup>10</sup> Unlike patent provisions for small molecule drugs, the patents protecting biologic innovation are not required to be made public.<sup>11</sup> As a result, biosimilar manufacturers either have to re-create the reference biologic on their own or rely on the private exchange of patent information between the reference and biosimilar manufacturers.<sup>12</sup> Furthermore, the BPCIA made it incumbent on the biosimilar competitor to disclose the contents of their FDA application to the reference

<sup>8</sup> Overpatented, Overpriced Curbing patent abuse: Tackling the root of the drug pricing crisis. (2022). In *I-MAK*. <https://www.i-mak.org/wp-content/uploads/2023/01/Overpatented-Overpriced-2023-01-24.pdf>

<sup>9</sup> Overpatented, Overpriced: How Excessive Pharmaceutical Patenting is Extending Monopolies and Driving up Drug Prices. (2018). *I-MAK*. <https://www.i-mak.org/wp-content/uploads/2018/08/I-MAK-Overpatented-Overpriced-Report.pdf>

<sup>10</sup> Dalpoas, S. E., Socal, M. P., Proctor, C. A., & Shermock, K. M. (2020). Barriers to biosimilar utilization in the United States. *American Journal of Health-System Pharmacy*, 77(23), 2006–2014. <https://doi.org/10.1093/ajhp/zxaa297>

<sup>11</sup> 42 U.S. Code § 262 - Regulation of biological products. (n.d.-b). LII / Legal Information Institute. [https://www.law.cornell.edu/uscode/text/42/262#:~:text=\(2\)%20The%20term%20%E2%80%9Cbiosimilar,in%20clinically%20inactive%20components%3B%20and](https://www.law.cornell.edu/uscode/text/42/262#:~:text=(2)%20The%20term%20%E2%80%9Cbiosimilar,in%20clinically%20inactive%20components%3B%20and)

<sup>12</sup> Dalpoas, S. E., Socal, M. P., Proctor, C. A., & Shermock, K. M. (2020). Barriers to biosimilar utilization in the United States. *American Journal of Health-System Pharmacy*, 77(23), 2006–2014. <https://doi.org/10.1093/ajhp/zxaa297>

manufacturer prior to seeking FDA approval, so that the reference manufacturer may determine if any relevant patent would be violated as a result of the biosimilar entering the market. Though this process was established with the goal of allowing for resolution between the originator and biosimilar manufacturers and reduce the risk of legal action, it creates opportunities for delay. In an attempt to discourage the extended use of the “patent dance” to purposefully delay the development of biologics, Congress passed the Purple Book Continuity Act of 2019, which went into effect in 2021 and is the first ever provision requiring public listing of certain biologic patents. The Act now requires manufacturers of reference biologics to publicly list certain patents for biologic products that they have confidentially disclosed to competitors as part of the “patent dance”. The Act stops short of full disclosure, and given the complex competitive dynamics at play, the resultant impact on new product market entry is yet to be understood,<sup>13</sup> potentially leading to further delays in biosimilar entry.

Janssen engaged in a prolonged “patent dance” with Celltrion, Inc., the drug manufacturer which sought to bring the first biosimilar infliximab (originally Remsima, but later branded as Inflectra) to market. Upon FDA approval in 2016, Inflectra was only the second ever biosimilar to be approved in the U.S. and was subject to significant legal maneuvering, which delayed its entry into the market. Even after launch, Inflectra continued to be mired in patent litigation stemming from the “patent dance” process.<sup>14</sup>

## Commercialization and Access

### *Market Factors*

Remicade is part of the 14% of the biologics market today that faces marketplace competition from approved and actively marketed biosimilars. In many ways, the introduction of biosimilars to compete with Remicade reflects traditional economic theory, that competition tends to drive prices down. In Figure 1, year-over-year growth in the wholesale acquisition cost (WAC) for Remicade flattened upon the 2016 introduction of its first biosimilar competitor, Inflectra. While this is the price a wholesaler pays to acquire a drug from the wholesaler’s supplier, typically the drug manufacturer, it is almost always higher than the price that the end customer or pharmacy pays the wholesaler for the drug, especially when it comes to generic drugs.

Since 2017, the WAC has remained relatively stable for all three infliximabs, including the 2018-introduced Renflexis. However, declining prices do not always translate into changes in market share or cost-savings for patients. According to one analysis of Medicare Part B claims conducted in 2018, two years after Inflectra and Renflexis launched, biosimilars captured ten percent of the infliximab market.<sup>15</sup>

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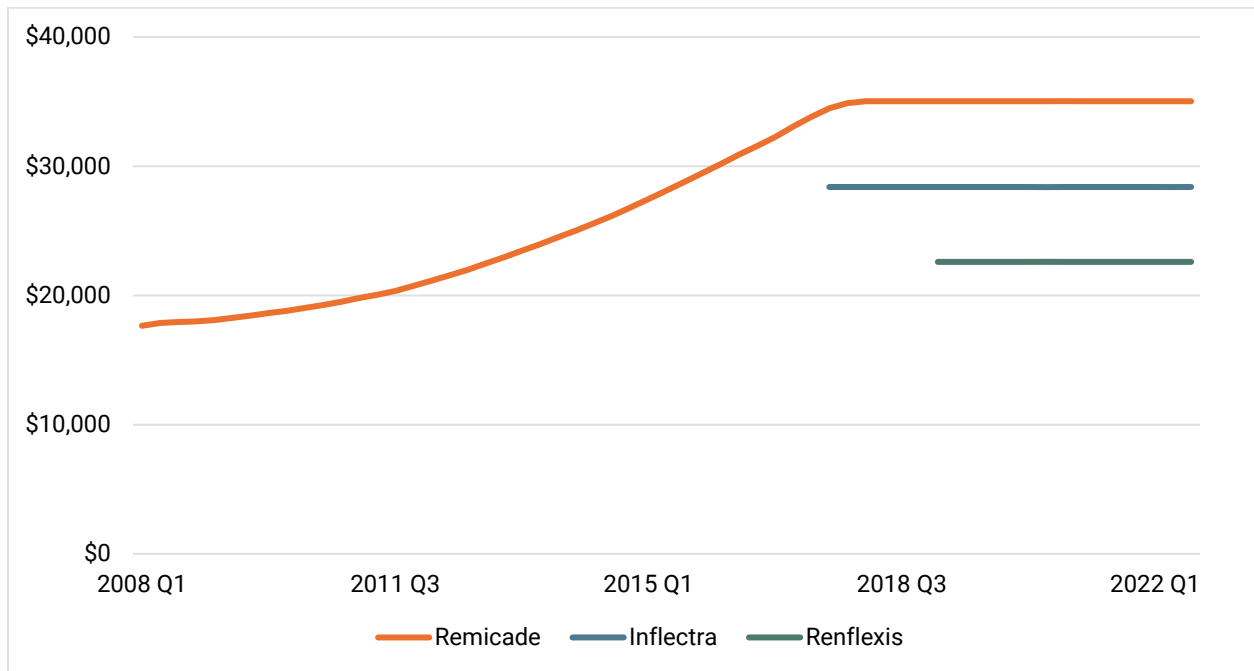
<sup>13</sup> *Changes to the Purple Book: Progress in Transparency*. (2021, August 3). JD Supra. <https://www.jdsupra.com/legalnews/changes-to-the-purple-book-progress-in-6749919/>

<sup>14</sup> Mehr, S. (2018, April 17). *Remicade’s patent declared invalid*. Biosimilars Review and Report. <https://biosimilarsr.com/2018/01/25/pfizers-inflectra-launch-pays-off/>

<sup>15</sup> Chen, A. P., Gascue, L., Ribero, R., & Herman, W. H. (2020). Uptake of Infliximab Biosimilars Among the Medicare Population. *JAMA Internal Medicine*, 180(9), 1255. <https://doi.org/10.1001/jamainternmed.2020.3188>

And recently, a 2023 IQVIA biosimilars report demonstrates that biosimilars today account for less than half (44%) of total infliximab volume.<sup>16</sup>

**Figure 1. Total WAC Cost per Year or Course<sup>17</sup>**



Source: Data from SSR Health.

Note: Cost per year or course of therapy is estimated by multiplying estimated price per unit at the product level by the maximum annual or course dosage included on the product's package insert assuming a U.S. patient of representative weight or body surface area, as determined using National Center for Health Statistics data

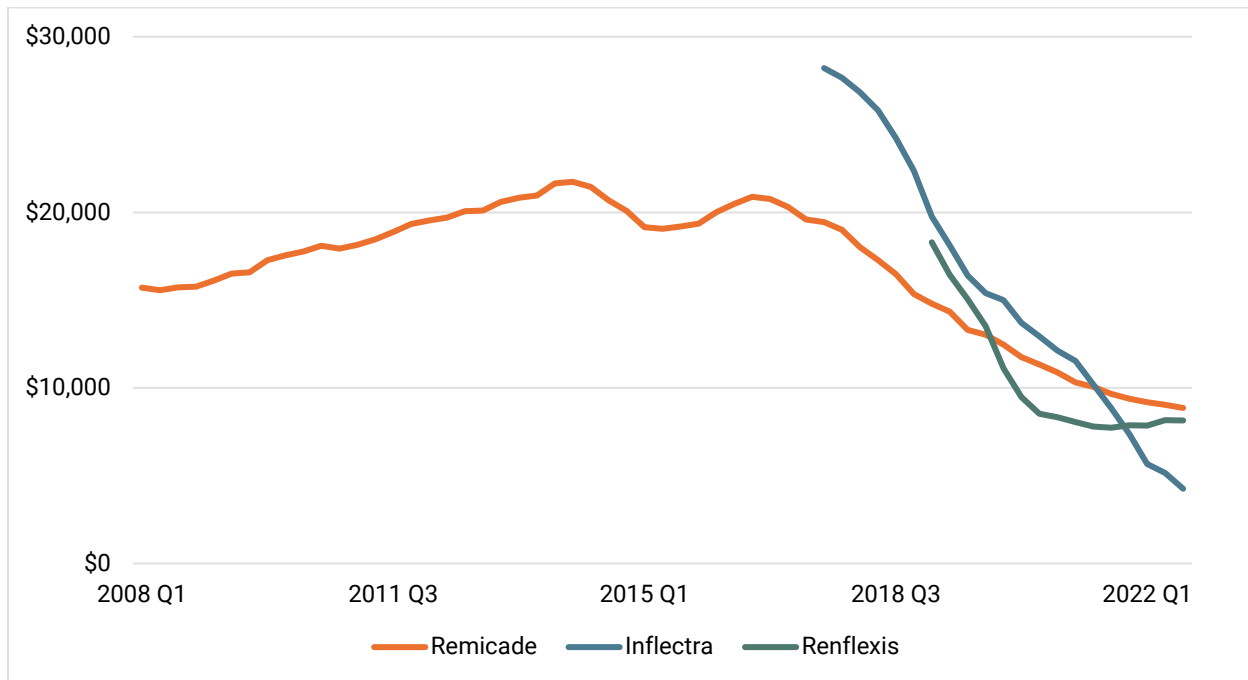
Analyzing how the WAC changes when competitors enter the market is an important indicator of market trends and can demonstrate the incentives throughout the supply chain that shape other pricing dynamics such as negotiated price discounts from health insurance companies and pharmacy benefit managers (PBM), as well as formulary contracting strategies. While WAC growth was stagnating, discounts for Remicade started to increase, thereby lowering Remicade's net cost. An increase in discount behavior is generally indicative of a manufacturer recognizing the need to increase its negotiation leverage with PBMs and payers to secure favorable formulary coverage. As shown in Figure 2, the net cost (WAC minus the dollar discount) of Remicade began to consistently decline around the end of 2016, as Remicade's manufacturer prepared for the approval and launch of Inflectra, the first-to-market biosimilar. Remicade's net price has continued to decline, along with the net prices of both

<sup>16</sup> Biosimilars in the United States 2023–2027. (2023). In IQVIA. <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/biosimilars-in-the-united-states-2023-2027/iqvia-institute-biosimilars-in-the-united-states-2023-usl-orb3393.pdf>

<sup>17</sup> Avsola data from SSR Health was unavailable at time of publication

Inflextra and Renflexis. As of Q3 2022, the net cost of Remicade had dropped to just under \$10,000 for a year, less than half of its 2014 net cost of \$22,000.

**Figure 2. Total Net Cost per Year or Course**



Source: Data from SSR Health.

Note: Cost per year or course of therapy is estimated by multiplying estimated price per unit at the product level by the maximum annual or course dosage included on the product's package insert assuming a U.S. patient of representative weight or body surface area, as determined using National Center for Health Statistics data

Following these price changes, in 2021, Remicade's manufacturer made available an unbranded infliximab, which is considered the same product as the brand name Remicade under the same biologics license issued at approval of Remicade by the FDA, but it came with a lower list price.<sup>18</sup> Janssen's introduction of this unbranded infliximab allowed the manufacturer to maintain market share with a lower priced medication and offered the possibility of providing a smaller rebate in contracting discussions with payers and PBMs than the higher-priced reference product.

### Regulation

<sup>18</sup> Janssen, I. C. W. (2022, December 13). Understanding Unbranded Biologics. *Beckerspayer*. <https://www.beckerspayer.com/payer/understanding-unbranded-biologics.html>

Physicians treating Medicare patients have traditionally been reimbursed a rate of the Average Sales Price (ASP)<sup>19</sup> plus six percent (ASP 6) of the reference biologic or biosimilar administered in an office setting. This changed in 2019, when CMS implemented a payment model modification under the Physician Fee Schedule whereby biosimilars were reimbursed on the basis of ASP 6 of the reference biologic, instead of on the basis of the ASP 6 of the biosimilar. This change was meant to create a meaningful economic incentive for physicians to prescribe a biosimilar, when clinically appropriate, as a substitute for the reference biologic.<sup>20</sup> This would increase the amount they earn from purchasing and administering a lower cost biosimilar, while getting reimbursed as if they purchased and administered the higher-priced reference biologic.

Then, more recently, the Inflation Reduction Act (IRA) created further economic incentives for physicians to choose the biosimilar by authorizing a five-year reimbursement increase of ASP plus eight percent (ASP 8) of the reference biologic for biosimilars.<sup>21</sup> The Center for Medicare and Medicaid Innovation (CMMI) is considering the development of additional focused payment models to further advance biosimilar adoption, which demonstrates CMMI's commitment to increasing biosimilar adoption.<sup>22</sup>

### *Distribution*

Payer contracting terms and strategies can also significantly influence distribution and price. According to one of the nation's largest Group Purchasing Organizations<sup>23</sup>, infliximab biosimilars are all on physician and hospital organizations' formularies, however, infliximab biosimilar market share tends to be lower relative to the market share of other biosimilars.<sup>24</sup> One potential reason for the lower-than-expected market share of infliximab biosimilars was the 2017 lawsuit between Janssen and the manufacturer of the Inflectra biosimilar, Pfizer Inc. (Pfizer). The lawsuit accused Janssen's parent company, Johnson & Johnson, of suppressing competition by implementing exclusionary contracts with both health insurers and provider organizations.<sup>25</sup> While the two companies settled their lawsuit in the summer of 2021,<sup>26</sup> the Federal Trade Commission (FTC) is further investigating Johnson & Johnson for its Remicade contracting strategies. The FTC is seeking to determine whether the company violated

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<sup>19</sup> Average Sales Price (ASP) is the volume-weighted average of the manufacturers' average sales prices for all National Drug Codes assigned to the drug or biological product. This number is statutorily defined and used the basis of Medicare reimbursement for pharmaceutical products.

<sup>20</sup> Dalpoas, S. E., Socal, M. P., Proctor, C. A., & Shermock, K. M. (2020). Barriers to biosimilar utilization in the United States. *American Journal of Health-System Pharmacy*, 77(23), 2006–2014. <https://doi.org/10.1093/ajhp/zxaa297>

<sup>21</sup> *A Report in Response to the Executive Order on Lowering Prescription Drug Costs for Americans*. (n.d.). U.S. Department of Health and Human Services. <https://innovation.cms.gov/data-and-reports/2023/eo-rx-drug-cost-response-report>

<sup>22</sup> Ibid.

<sup>23</sup> A group purchasing organization (GPO) is an entity that helps healthcare providers — such as hospitals, nursing homes and home health agencies — realize savings and efficiencies by aggregating purchasing volume and using that leverage to negotiate discounts with manufacturers, distributors and other vendors.

<sup>24</sup> *New Survey from Vizient Provides Hospital Insights into Biosimilar Adoption and What is Preventing Greater Utilization*. (2022, November 30). Vizient Newsroom. <https://newsroom.vizientinc.com/en-US/releases/new-survey-from-vizient-provides-hospital-insights-into-biosimilar-adoption-and-what-is-preventing-greater-utilization>

<sup>25</sup> Pfizer, Johnson & Johnson settle high-profile Remicade biosim lawsuit on undisclosed terms. (2021, July 26). *Fierce Pharma*. <https://www.fiercepharma.com/pharma/pfizer-johnson-johnson-agree-to-a-settlement-terms-undisclosed-biosimilar-lawsuit>

<sup>26</sup> Ibid.



antitrust laws when it set up a variety of exclusionary contracts, including those with hospitals that bundled much of Johnson & Johnson's drugs and devices including Remicade.<sup>27</sup>

Other contracting strategies with payers include preferred tier 1 formulary placement, meaning that treatment with Remicade must be the patient and provider's first choice before the payer and PBM would authorize use of an infliximab biosimilar.<sup>28</sup> PBMs place medicines like Remicade on tier 1 in a preferred fashion in exchange for meaningful rebates. Rebates between manufacturers and PBMs (and by extension, payers) play a consequential, largely invisible role when it comes to the actual prices paid by providers and patients for biologics and biosimilars. Rebates are off-invoice amounts paid by manufacturers to PBMs after the point of sale and can make up 40% or more of the drug's list price.<sup>29</sup> It can be difficult to assess exact rebate amounts or terms, as there are no uniform reporting or disclosure requirements in place. In the case of a biologic facing the prospect of a biosimilar new market entry, the reference biologic manufacturer may offer a rebate to a PBM such that the final price paid by the PBM for the reference biologic is less than the list price of the biosimilar, thus incentivizing the PBM to keep the biosimilar off its formulary or on a non-preferred tier.

## Patient Implications

*Note: Patient scenarios are meant to be illustrative only. The goal of these scenarios is to demonstrate the patient experience while accessing their medications and the ways manufacturer pricing and contracting incentives impact patient access. Prices are based on publicly available information when possible (and cited accordingly) and based on good-faith estimates when prices were not available.*

In the scenarios below, we follow the journey of a 55-year-old patient with Crohn's disease with a high-deductible health plan through employer-sponsored insurance. These scenarios will differ based on the design of the formulary and tiers of the PBM for her employer-sponsored insurance. This difference will impact her ability to access a biosimilar and result in substantially different out-of-pocket drug costs for the patient.

### Scenario 1

The patient's PBM has placed Remicade (biologic) into a preferred formulary tier because of its contract with Remicade's manufacturer and negotiated discounts (rebates) off of Remicade's list price. Additionally, the biosimilar, Renflexis, has been placed into a non-preferred formulary tier. As a result of formulary tiering, Remicade is prescribed to the patient. The WAC, or list price, for a year of Remicade as of Q3 2022 was approximately \$35,000. The patient will first pay her \$3,000 deductible (if not already met), and then will be responsible for a 20% patient coinsurance on the remaining cost of the

<sup>27</sup> J&J boasted about defending Remicade from biosims. Now it's under FTC investigation. (2019, July 30). *Fierce*

*Pharma*. <https://www.fiercepharma.com/pharma/j-j-has-boasted-about-its-remicade-defense-and-now-it-s-under-ftc-investigation>

<sup>28</sup> Dalpoas, S. E., Socal, M. P., Proctor, C. A., & Shermock, K. M. (2020a). Barriers to biosimilar utilization in the United States. *American Journal of Health-System Pharmacy*, 77(23), 2006–2014. <https://doi.org/10.1093/ajhp/zxaa297>

<sup>29</sup> Seeley, E., & Kesselheim, A. (2019b). *Pharmacy Benefit Managers: Practices, Controversies, and What Lies*

*Ahead*. <https://www.commonwealthfund.org/publications/issue-briefs/2019/mar/pharmacy-benefit-managers-practices-controversies-what-lies-ahead>

drug. In sum, the patient's out-of-pocket for the year (deductible plus coinsurance) is \$9,400, which breaks down to a monthly average cost of \$783.

## Scenario 2

In the absence of any exclusionary contracts, the patient's PBM has placed both Remicade and a biosimilar, Renflexis, into an equivalent formulary tier. As a result of equivalent tiering, and due to Renflexis' lower price, the patient receives a prescription to Renflexis. The WAC, or list price, for a year of Renflexis as of Q3 2022 was approximately \$22,500. The patient will first pay her \$3,000 deductible (if not already met), and then will be responsible for a 20% patient coinsurance on the remaining cost of the drug. In sum, the patient's out-of-pocket for the year (deductible plus coinsurance) is \$6,900, which breaks down to a monthly average cost of \$575.

Scenario 1	Scenario 2
Remicade (biologic)	Renflexis (biosimilar)
Due to PBM-manufacturer contracting and subsequent formulary tiering, the patient is prescribed Remicade.	Due to the absence of PBM-manufacturer exclusionary contracts, the patient is prescribed Renflexis
Assuming the patient has not met their annual deductible, patient is responsible for deductible of \$3,000 plus 20% coinsurance on the remaining cost.	
The patient's out-of-pocket for the year is \$9,400, which breaks down to a monthly average cost of \$783.	The patient's out-of-pocket for the year is \$6,900, which breaks down to a monthly average cost of \$575.

## Conclusion

Biosimilars offer a compelling alternative to reference biologics, not only because they increase the potential pool of clinical solutions for patients with complex conditions, but because they may also introduce competition into a market with traditionally high prices. However, as detailed in this playbook, delayed entry of biosimilars due to patent maneuvering, contracting strategies employed by manufacturers of reference biologics, and provider payment incentives and preferences, combine to slow the uptake of biosimilar adoption. While there have been some regulatory steps put in place to reverse this trend, a variety of market dynamics prevent the U.S. health care market from realizing the full potential of biosimilar competition.

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