IMMUNOLOGY TO ONCOLOGY:

A STUDY OF BIOSIMILAR MARKET EVOLUTION

Policy Reporter

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Introduction

Biologics play an essential role in healthcare and currently represent about $232 billion in global revenue, an estimated 25% of the entire world pharmaceutical market [1]. The US biologics market is estimated at $86.5 billion in 2020 [2]. In recent years, the US market has experienced a significant increase in FDA approvals for biologics. Much of this growth was seen in the treatment of cancer. Of the 22 new biologics approved in 2020, 11 of them were for cancer treatment [3]. Biologic drugs have represented a pioneering step in the treatment of cancer, owing much to their comparatively mild side-effect profile compared to traditional chemotherapy [4].

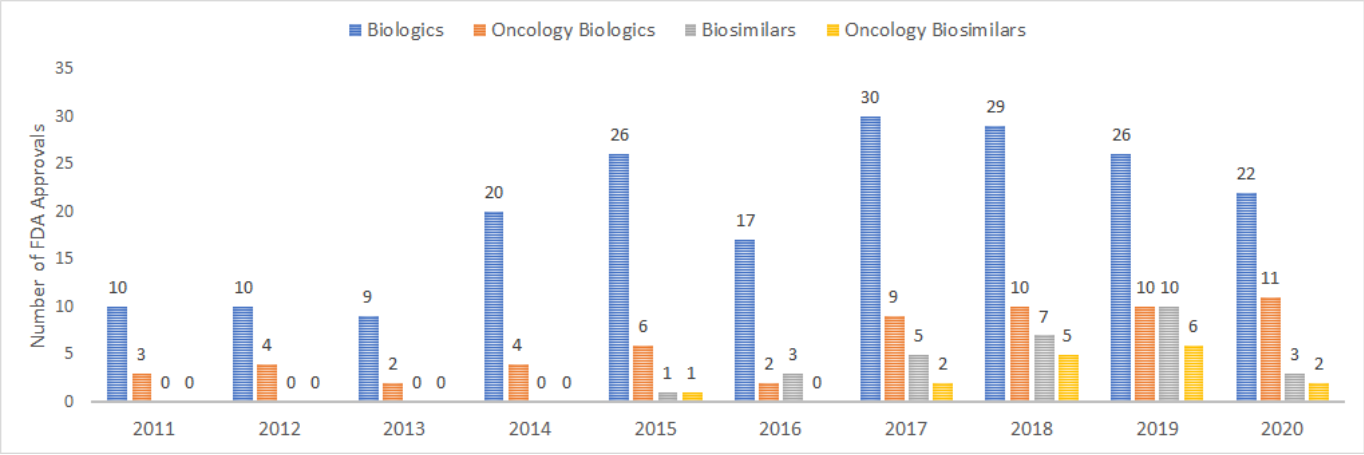


Figure 1: Number of FDA Approvals

As examined in the previous edition of this biosimilar publication series, Insights into the Market for Infliximab [6], neither prescribers nor health plans have been particularly friendly to biosimilar products in the market for infliximab. Prescribers demonstrate a marked preference for prescribing the infliximab reference product, Remicade® (Janssen Biotech, Inc.). Leonard et al. (2019) performed a systematic review to evaluate U.S. healthcare providers' acceptance and prescribing behavior for biosimilars. They reviewed 158 citations published between 2014 and 2018 and found that U.S. healthcare providers are cautious in prescribing biosimilars [6]. In our analysis of proprietary Policy Reporter data, we also observed health plans frequently accommodating that preference by including Remicade as a preferred drug, even when a biosimilar is also assigned preferred status [Appendix b]. Even four years post-US market launch, Inflectra® and Renflexis® (manufactured by Pfizer and Merck, respectively) have a combined share of only 16% as of July 2020 [7]. Limited acceptance of biosimilars by prescribers and payers' acquiescence to prescribers' preferences have effectively combined to curb adoption. See Figure 2.

However, our analysis of the oncology market reveals that early dynamics may evolve into a different equilibrium than did the market for infliximab. As the manufacturers of the oncology biologics have had the opportunity to observe the first year of the infliximab market, they may have adjusted their strategies. Additionally, the same manufacturer of reference products has released second generation biologics and may be focusing its efforts on marketing those products. Since oncolytics are acute treatment (rather than for chronic treatment), physicians may be less hesitant to transition to the use of biosimilars than are prescribers of infliximab, which is used for chronic conditions. Finally, additional legislation surrounding biosimilars may further influence the market.

This publication explores how the oncology biosimilar markets were informed by the dynamics of the market for infliximab and how the similarities and dissimilarities between these markets may affect pricing, market share and patient access.

Lessons from Infliximab for the Oncology Biosimilar Markets

The Remicade market experienced aggressive price competition after biosimilar products gained traction contracting with health plans for preferred product status. This traction is demonstrated by access to covered lives at health plans that named a preferred product. As the first launched infliximab biosimilar product, Inflectra grew its covered lives access to 52% between 3Q 2019 and 3Q 2020 [5].

Since Remicade was the first biologic for autoimmune conditions to face biosimilar competition, there was no roadmap within the therapeutic class for the manufacturers of either Remicade or Inflectra to follow when setting price. After Inflectra launched at 123% of Remicade's ASP, Inflectra's pricing better reflected market dynamics after it had been on the market for two quarters. When the second infliximab biosimilar (Renflexis) launched, both Renflexis's and Inflectra's prices were 87% of Remicade's ASP. Inflectra and Renflexis both reached their lowest prices relative to Remicade eight quarters after Inflectra's launch (four quarters after Renflexis launched), at 73% and 80% of Remicade's price, respectively. In response in subsequent quarters, Remicade's pricing decreased faster than did the biosimilars', and as of Q4 2020, Remicade's price was less than 10% higher than that of Inflectra or Renflexis. Remicade's aggressive price competition beginning six quarters after Inflectra's launch may have been a delayed response to the drastic drop in Inflectra's price, a reaction to the entry of the second biosimilar at ASP parity with Inflectra, or a response to Inflectra's growing access to covered lives. See Figure 2.

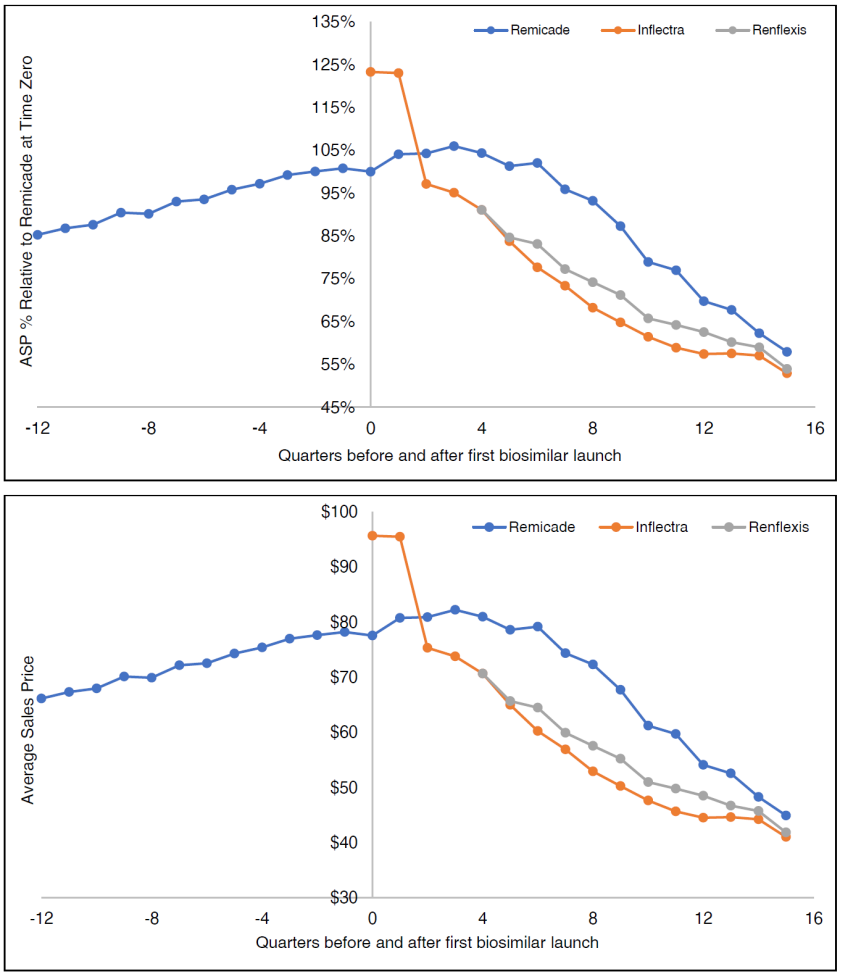
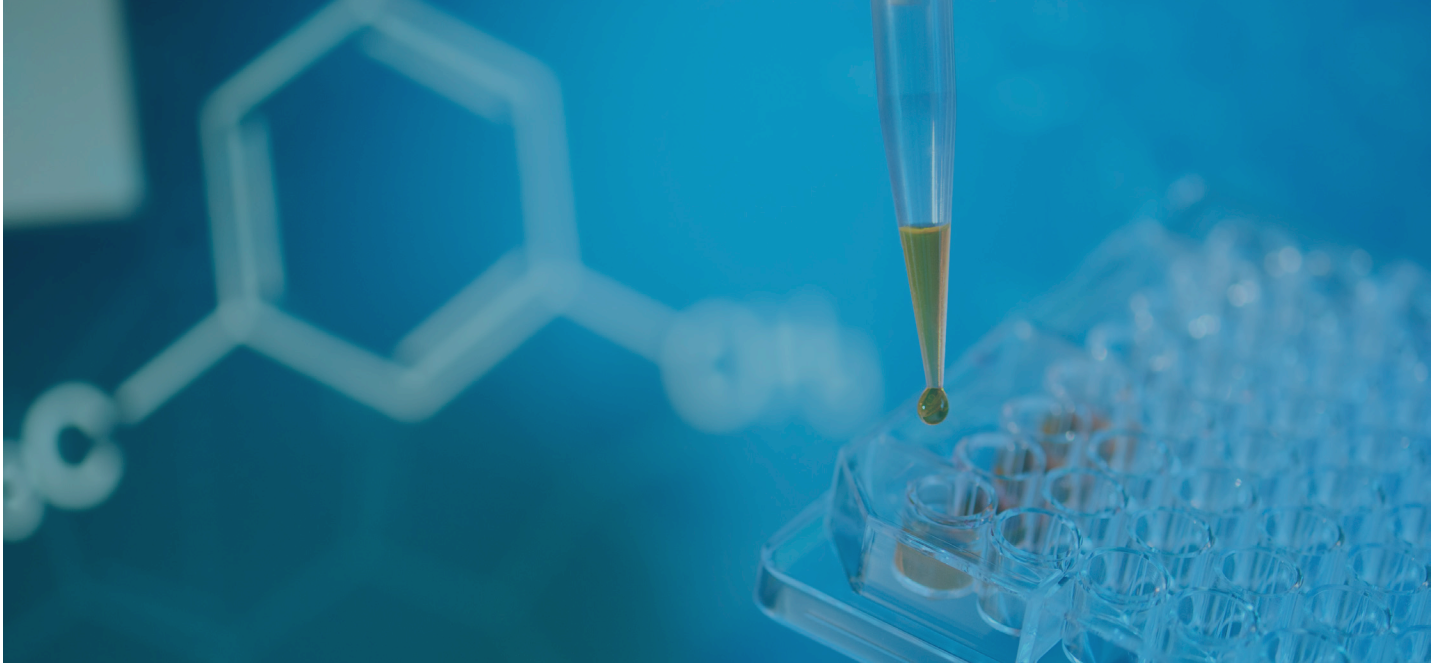


Figure 2: Remicade and Its Biosimilars



Notwithstanding that delay, because of ASP reductions for Remicade, health plans regularly named it as a preferred product while also naming a biosimilar preferred, granting Remicade consistent access to more than 90% of covered lives. This allowed healthcare professionals to continue prescribing according to their preference for Remicade when it was available, particularly for patients who were already stable on it. A survey by Gibofsky and McCabe (2020) demonstrated that a minority of prescribers (35%) were likely/very likely to switch to a biosimilar for a patient with rheumatoid arthritis who was already established on treatment with Remicade. Additionally, for a patient with a different rheumatological condition than the one on which the biosimilar's approval was based (i.e., a condition indicated via extrapolation), only 40% of survey respondents were likely/very likely to initiate biosimilar treatment, and only 21% were likely/very likely to switch to a biosimilar if the patient was doing well on the reference product [8]. As a result, increases in access to health plan covered lives for infliximab biosimilars was poorly correlated with increases in market share, as seen above in the limited combined share of Inflectra and Renflexis.

Nevertheless, savings in medical spend are available to health plans for infliximab products. In a study focusing on cost savings for large employers, Socal et al. (2020) found that, when matched for all characteristics, biosimilar infliximab offered a median discount of 32% over Remicade [9]. A study from the University of Utah found that switching patients from Remicade to an infliximab biosimilar resulted in an average savings of $11,508 per patient for the University of Utah Health Plans [10]. Still, because of physician preference for Remicade and the fact that access to covered lives for infliximab biosimilars coincided with ongoing access to Remicade (at 90% of covered lives in 2020), in order for biosimilar products to accelerate their development of market share, health plans will likely have to exclude Remicade from preferred status.

The Influence on Oncology

The oncology biosimilar market is currently composed of three entities: trastuzumab (Herceptin), rituximab (Rituxan), and bevacizumab (Avastin). The FDA has approved five biosimilar trastuzumab products since 2017, the first being Ogivri® (Mylan), with four more between 2018 and 2019: Herzuma® (Celltrion), Ontruzant® (Samsung Bioepis), Trazimera™ (Pfizer) and Kanjinti™ (Amgen). Three rituximab biosimilars have been approved since 2018: Truxima (Teva/Celltrion) in 2018, Ruxience (Pfizer) in 2019, and Riabni (Amgen/Allergan) in 2020. Two bevacizumab biosimilars have been approved: Mvasi (Amgen/Allergan) in 2017 and Zirabev (Pfizer) in 2019. This publication addresses all three reference products but uses trastuzumab as a primary example of certain market conditions.

Our data show that, while the price peak for Remicade in the infliximab market occurred three quarters after launch of the first biosimilar, the oncolytic reference products' highest prices occurred prior to the launch of each product's first biosimilar. Herceptin and Avastin reached their highest prices two quarters and one quarter prior to launch, respectively; Rituxan's highest price was four quarters prior to the launch of its first marketed biosimilar, Truxima. Since then, prices for the oncology reference products have declined slowly. Herceptin and Avastin had average price decreases of 1.67% per quarter and 1.52%, respectively (CAGR), while prices for their first marketed biosimilars, Kanjinti and Mvasi declined 3.6% and 3.46%. See Figure 3.

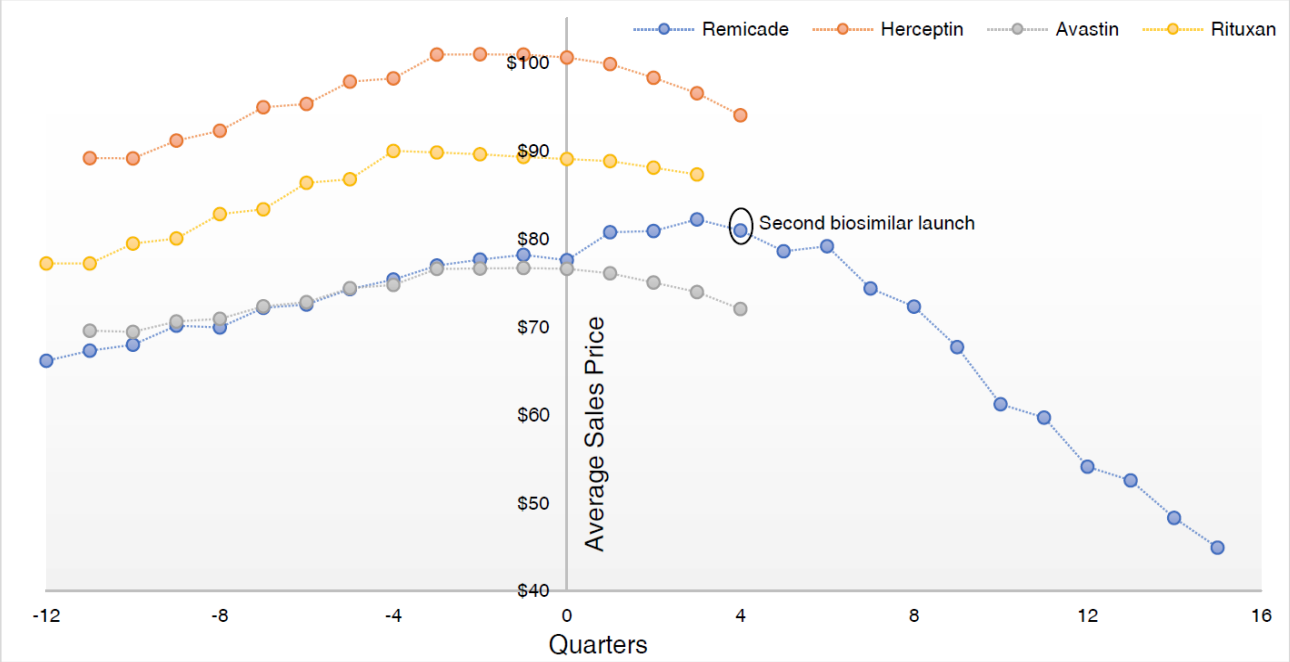


Figure 3: Change in ASP Pricing of Oncolytic Reference Products (Herceptin, Avastin and Rituxan) in Comparison to Remicade

Rituxan is unique among the oncology biologics since it is also indicated for rheumatoid arthritis (RA). At launch, Truxima was approved for Rituxan's oncology indications (non-Hodgkin's lymphoma [NHL], chronic lymphocytic leukemia [CLL]), and a rare inflammatory condition (polyangiitis), but only became fully competitive when it was approved for RA in May of 2020. The later entrant into the rituximab market, Ruxience, is only indicated for NHL, CLL, and polyangiitis. Rituxan's price has decreased even more slowly than the other reference products since its peak, dropping 1% between its highest point and the launch of Truxima, and an additional 2% over the three quarters since launch. Truxima dropped an average of 8.04% per quarter (on a CAGR basis) during its first year on the market. See Figure 4.

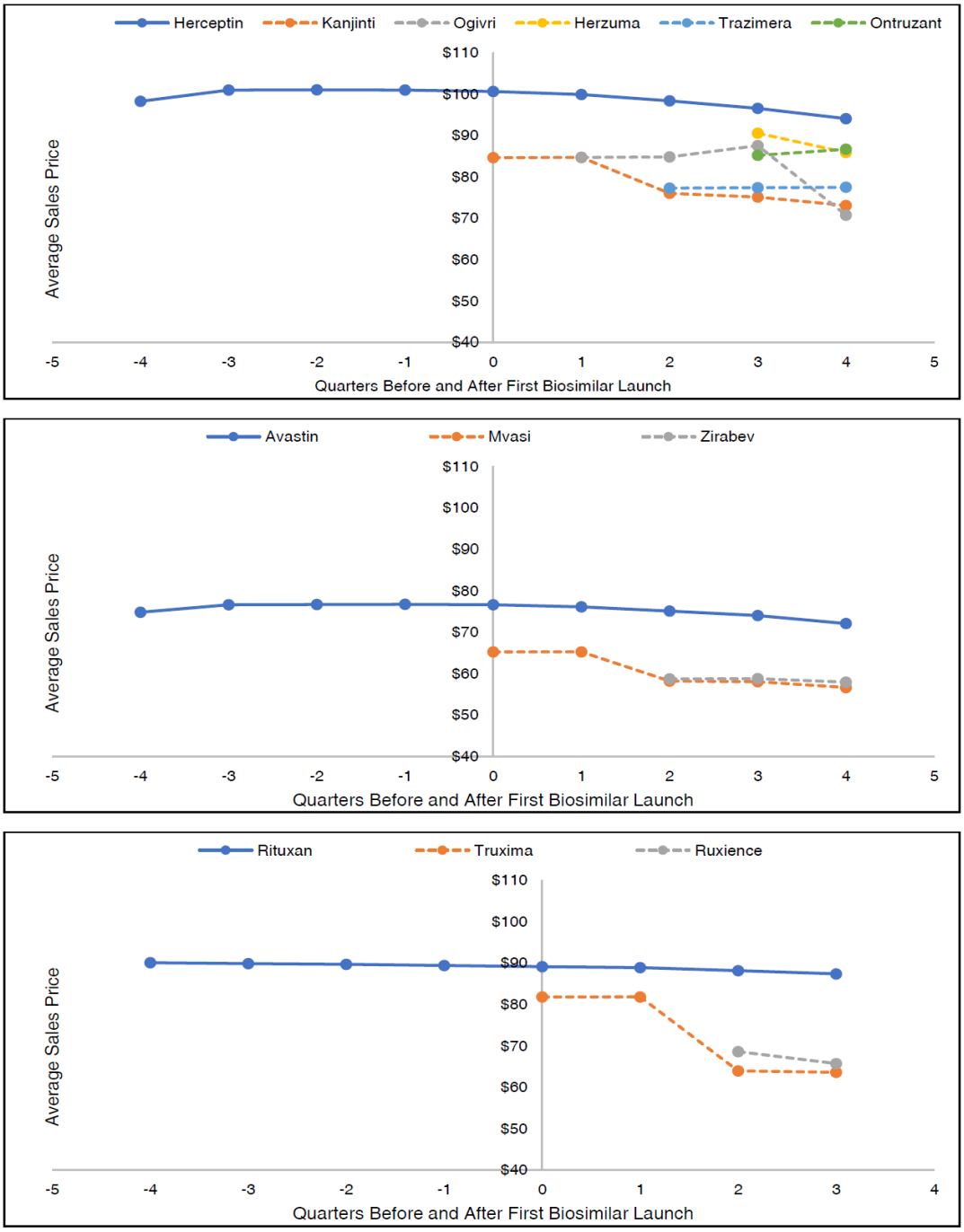


Figure 4: Change in ASP Pricing of Oncolytic Reference Products (Herceptin, Avastin and Rituxan) in Comparison to Their Biosimilars

Manufacturers of oncolytic biosimilars may have learned lessons from the early quarters after Inflectra's launch, too. The first biosimilar of each oncolytic entered the market at a lower price than the reference product, indicating that rebate contracts with health plans were aggressively negotiated and effective at launch. This also explains the peaking of reference products ASPs' before biosimilar launches. Kanjinti entered at 84% of Herceptin's price, Mvasi at 85% of Avastin's price, and Truxima at 92% of Rituxan's price. All three have so far seen continual decreases, at twice the rate or more of the reference products' rates. In the four quarters since launch, Kanjinti has dropped its price to ~22% discount to Herceptin. Other trastuzumab biosimilar manufacturers may have little motivation to further lower their prices; as shown in Figure 6, Kanjinti almost immediately gained access to more covered lives than Herceptin had. In the next section we explore why that may be the case.

Oncology Market Dynamics and Biosimilar Markets

Herceptin is a HER2/neu receptor antagonist indicated for the treatment of HER2-overexpressing metastatic breast cancer, adjuvant treatment of HER2-overexpressing breast cancer, and the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma [11]. Biosimilar products do not always carry all the indications of the reference product; indications are assigned based upon FDA processes for extrapolation, which require scientific justification factors including knowledge of the mechanism(s) of action, pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity of the reference product in each of its approved indications [fda.gov]. However, all trastuzumab biosimilar products hold the same indications, making the biosimilars fully equivalent to the reference product from a use perspective. The same is not true for rituximab and bevacizumab biosimilars. Ruxience and Riabni are approved for Rituxan's oncology indications and polyangiitis, but not RA. While Truxima is now approved for RA, at launch it was only approved for oncology indications. Of the rituximab biosimilars, none are approved to treat pemphigus vulgaris (PV). Mvasi and Zirabev both lack Avastin's hepatocellular carcinoma indication, and Mvasi is not approved for epithelial ovarian, fallopian tube, or primary peritoneal cancer [12-18].

This equivalence, or lack thereof, has influenced how health plans are managing trastuzumab biosimilars. Figure 5 shows the change in health plan covered lives that are subject to coverage limitations for trastuzumab. This figure accounts for health plans that have named trastuzumab preferred products (i.e., one or more trastuzumab products require trial of the preferred trastuzumab) versus plans that have no preferred products (i.e., all available trastuzumab products have equal access). The change is shown for the period of Q4 2019 to Q4 2020 and represents coverage by ten of the top payers as defined by total covered lives across Commercial, Medicare Advantage and Managed Medicaid lines of business [Appendix A]. Following the launch of all currently marketed trastuzumab products, more than one third of health plan covered lives became subject to preferred product coverage limitations, a steep increase from Q4 2019.

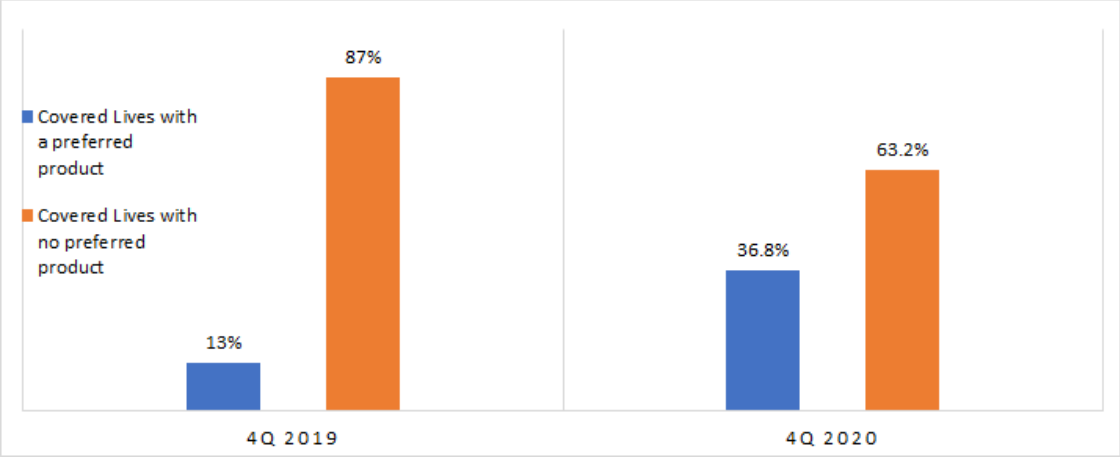


Figure 5: Trastuzumab Covered Lives Subject to Preferred Product Designation

The rate of adoption of preferred products in the trastuzumab market, as demonstrated in Figure 5, indicates an early willingness on the part of health plans to implement preferred brands in this market. This change has occurred specifically because biosimilars have increasingly been named as preferred products. Figure 6 shows that, because of health plans that have named no preferred product or have named a biosimilar as preferred, trastuzumab biosimilars' access to covered lives has increased significantly. As of 4Q 2020, Herceptin has access to only 15% of 159M covered lives, eclipsed by two biosimilar products, Kanjinti (25%) and Trazimera (21%).

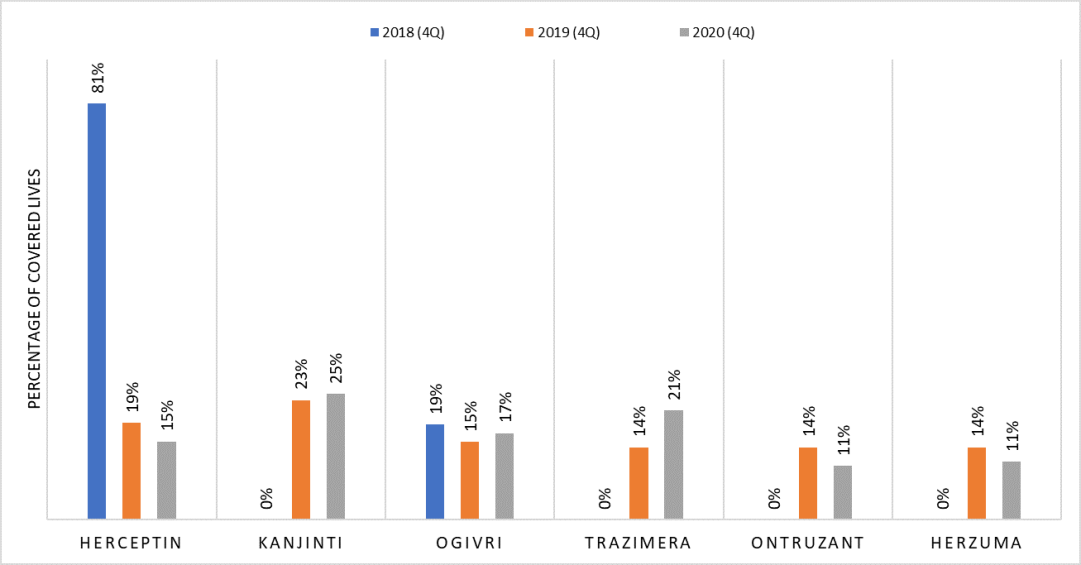


Figure 6: Covered Lives Access for Trastuzumab Products, 2018 - 2020

With a maturing market and the experience of both health plans and prescribers with biosimilar products in other areas of oncology (i.e. biosimilars of Neupogen®(filgrastim) have been safely used in supportive breast cancer treatment for over ten years [19]), payers are now willing to name preferred products without including the reference product. Health plans would not be able to engage in that strategy without acceptance of biosimilar products within their prescribing networks, likely driven by confidence of safety/efficacy. Otherwise it would not be clinically responsible to limit access to reference products.

Pricing

Given the lag in Remicade's price drop, the first four quarters of Remicade pricing did not prove to be representative of its eventual strategy. In Figure 7, note the divergence between the four quarter trend and the actual pricing illustrated by the solid blue line. Clearly, the first four quarters of data would not have been helpful to forecast Remicade pricing as the infliximab market developed. So, given that we only have four quarters of pricing history in the oncology market, how is its trend instructive? First, dollar decreases for oncology reference products, though small, started earlier than Remicade's, i.e. prior to launch rather than six quarters post-launch. So, even only based upon the first four quarters post launch, we have actually had eight quarters of pricing signals. Should Genentech continue price discounting in line with current trend (as seen in Figure 7)--and there's no early indication that it won't, its behavior would closely match Janssen's with Remicade and potentially mitigate loss in market share despite facing prior failure requirements.

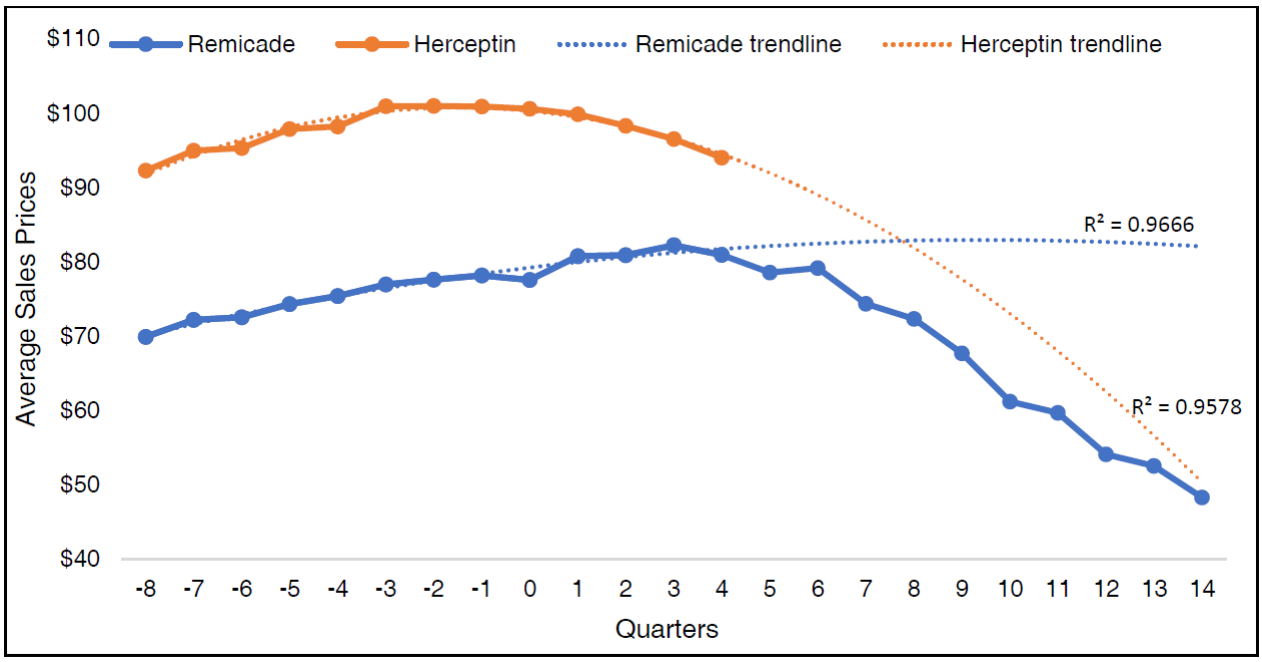


Figure 7: Projected ASP Trends

It is important to remember, however, that there is no guarantee Genentech will continue accelerating discounts the way Janssen did.

In mid-2020, Genentech launched Phesgo™, a second-generation product combining trastuzumab, pertuzumab, and hyaluronidase. Phesgo is approved for use (1) in combination with chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen or the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence; or (2) for use in combination with docetaxel for the treatment of adult patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease [20]. While all are approved for treatment of HER2-positive breast cancer, Phesgo's indications differ from Herceptin's and the trastuzumab biosimilars. Trastuzumab is indicated for adjuvant rather than neoadjuvant breast cancer treatment, and Phesgo lacks the gastric cancer indication of Herceptin and its biosimilars.

In Q4 2020, only six months after launch, Phesgo had access to 100% of covered lives for health plans that had published policies for Phesgo. However, many plans have not yet established coverage positions, particularly for Medicare Advantage or Managed Medicaid lines of business. Given the immediate ubiquity of covered lives with access to Phesgo, Genentech has the option to decrease Herceptin's price at a rate that maintains a constant premium to biosimilars, rather than accelerate to reduce it. Pricing data are not yet available, as Phesgo was only assigned a HCPCS code effective January 1, 2021 [21].

Biosimilar Legislation

In recent years, laws and legislation in the United States have encouraged acceptance of biosimilars. A total of 45 states now have biosimilar substitution laws dictating when a pharmacist has the authority to substitute a reference biologic with a less expensive biosimilar [22]. These include whether a prescriber and/or patient must be notified of substitution and whether the treater (person responsible for furnishing the drug at the site of care) must maintain records of substitution. It is worth noting that, among those 45 states, all except Kansas require an FDA certification of interchangeability before treaters can make any substitution. However, no biosimilars have yet been certified as interchangeable with the reference product [23]. When that happens, the states are positioned to allow treaters to work directly with patients to secure access to whichever product is the most cost-effective option.

In another effort to streamline biosimilar approval, the Coronavirus Response and Relief Supplemental Consolidated Appropriations Act of 2021 incorporated many healthcare-related provisions, including amendments to the Public Health Service Act, which applies to an abbreviated marketing pathway for biosimilars. Applications for new biosimilar products now "*may* [emphasis added] include information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product." That level of information was previously mandatory [24].

Additionally, in November 2020 the FDA released a draft guidance with questions and answers regarding biosimilarity and interchangeability. While the guidance has not yet been implemented, it does answer questions regarding the licensure of an interchangeable biosimilar [25]. Separate FDA guidance titled "Considerations in Demonstrating Interchangeability with a Reference Product" includes subjects such as data and information needed to support a demonstration of interchangeability [26]. With the FDA requirements for interchangeability made clearer, licensure of products may be smoother, increasing the number of options on the market, thereby offering prescribers and patients more options and potentially releasing treaters at all sites of care where the drug may be professionally administered to recommend substitution.

Summary

Data from health plan covered lives, as well as research on prescriber and patient attitudes toward biosimilars, show that infliximab biosimilars face challenges to adoption, made more severe by health plan decisions to include prescribing access to the reference product. This limited acceptance of Remicade biosimilars emphasizes the importance of go-to-market strategy for product adoption (favorable contracting, providers' acceptance, product education, etc.) and price competition. To maintain Remicade's share, Janssen offered discounts and rebates resulting in a 45.4% ASP drop over three years, from 4Q17 to 4Q20, which likely contributed to health plans' continued preference for Remicade over biosimilars.

Conversely, the data indicate that oncolytic biosimilar drugs are being adopted at a faster pace. Mvasi™ (Amgen) and Zirabev™ (Pfizer) have captured approximately 39% and 4% market share from Avastin. Herceptin is also experiencing fierce competition from its biosimilars, of which Kanjinti has the largest US market share (~32%). A similar trend is observed in supportive care drugs; sales revenue declined for the reference products--28% for Neulasta, 35% for Neupogen, and 28% for Epogen from 2Q 2019 to 2Q 2020--because of biosimilar competition [27].

Our analysis of the oncology market shows earlier, more dramatic gains in access by biosimilar products compared to the infliximab market. In other biosimilar markets where the reference product's access to covered lives and/or market share has been eclipsed by biosimilar products, such as the market for filgrastim, the marketer of the reference product is focusing on the success of a later generation product. Early data for Phesgo indicate we may see the same strategy from Genentech in response to price competition from trastuzumab biosimilars. More maturity in the ASP data is needed to clearly demonstrate how price competition in the oncology market has impacted brand marketing results.

Another aspect of this market to consider is the evolving sophistication of health plans. Health plans appear to be more willing to limit prescriber access to reference products in the oncology market, even in the early years of biosimilar product marketing. Prescribers are less inclined to object to brand preferences imposed by health plans when treating biologic naïve patients, though there is still resistance to non-medical switching from a reference product to a biosimilar [28]. All these factors drive a greater level of price competition and an opening for biosimilar products to build market share.

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Appendices

		Commercial			Medicare Advantage			Managed Medicaid		
		2018	2019	2020	2018	2019	2020	2018	2019	2020
Aetna	21,765,112	Y	Y	Y	N	Y	Y	Y	Y	Y
Anthem	32,034,067	N	Y	Y	N	Y	Y	N	Y	Y
BCBS Federal Employee Plan	6,147,885	Y	Y	Y	N	N	N	N	N	N
BCBS Florida	4,439,906	Y	Y	Y	Y	Y	Y	N	N	N
Centene	15,793,622	Y	Y	Y	N	N	Y	Y	Y	Y
Cigna	14,567,412	N	Y	Y	N	N	Y	N	N	N
HCSC	16,712,535	Y	Y	Y	Y	Y	Y	Y	Y	Y
Highmark Inc.	4,625,811	Y	Y	Y	Y	Y	Y	N	N	N
Humana	6,174,085	N	Y	Y	N	Y	Y	N	Y	Y
United Healthcare	37,332,545	N	Y	Y	N	N	N	N	N	N

Appendix A

List of Payers and Lines of Business used in the study.

Top 10 Payers: Trastuzumab Coverage Status (Total)

Product	2018 (4Q)		2019 (4Q)		2020 (4Q)		Coverage status (Preferred and No Preferred status included)
	Covered Lives	Covered Lives %	Covered Lives	Covered Lives %	Covered Lives	Covered Lives %	
Herceptin	65,763,217	81%	118,098,961	19%	81,595,136	15%	Covered lives that name Herceptin
Kanjinti	0	0%	145,654,840	23%	131,287,878	25%	Covered lives that name Kanjinti
Ogivri	15,080,292	19%	94,472,463	15%	90,273,530	17%	Covered lives that name Ogivri
Trazimera	0	0%	88,298,378	14%	113,841,561	21%	Covered lives that name Trazimera
Ontruzant	0	0%	88,298,378	14%	56,234,459	11%	Covered lives that name Ontruzant
Herzuma	0	0%	88,298,378	14%	60,674,365	11%	Covered lives that name Herzuma
Total	**80,843,509**	**100%**	**623,121,398**	**100%**	**533,906,929**	**100%**	

Top 10 Payers: Trastuzumab Coverage Status (Preferred status)

Product	2018 (4Q)		2019 (4Q)		2020 (4Q)		Coverage status
	Covered Lives	Covered Lives %	Covered Lives	Covered Lives %	Covered Lives	Covered Lives %	
Herceptin	50,682,925	63%	24,953,311	4%	25,360,677	5%	Covered lives that name Herceptin as trastuzumab preferred
Kanjinti	0	0%	52,509,190	8%	75,053,419	14%	Covered lives that name Kanjinti as trastuzumab preferred
Ogivri	0	0%	1,326,813	0%	34,039,071	6%	Covered lives that name Ogivri as trastuzumab preferred
Trazimera	0	0%	0	0%	57,607,102	11%	Covered lives that name Trazimera as trastuzumab preferred
Ontruzant	0	0%	0	0%	0	0%	Covered lives that name Ontruzant as trastuzumab preferred
Herzuma	0	0%	0	0%	4,439,906	1%	Covered lives that name Herzuma as trastuzumab preferred
Total	**50,682,925**	**63%**	**78,789,314**	**13%**	**196,500,175**	**37%**	

Top 10 Payers: Trastuzumab Coverage Status (No preferred Product)

Product	2018 (4Q)		2019 (4Q)		2020 (4Q)		Coverage status
	Covered Lives	Covered Lives %	Covered Lives	Covered Lives %	Covered Lives	Covered Lives %	
Herceptin	15,080,292	19%	93,145,650	15%	56,234,459	11%	Covered lives that do not name any preferred product
Kanjinti	0	0%	93,145,650	15%	56,234,459	11%	
Ogivri	15,080,292	19%	93,145,650	15%	56,234,459	11%	
Trazimera	0	0%	88,298,378	14%	56,234,459	11%	
Ontruzant	0	0%	88,298,378	14%	56,234,459	11%	
Herzuma	0	0%	88,298,378	14%	56,234,459	11%	
Total	**30,160,584**	**37%**	**544,332,084**	**87%**	**337,406,754**	**63%**	

Appendix B

Coverage status based on Health policies preference towards a specific