The Changing Biosimilar Landscape

Many cutting-edge biologic medications available today bring new hope to patients suffering from a variety of medical conditions including some types of cancers, multiple sclerosis as well as inflammatory diseases like rheumatoid arthritis, Crohn's disease, and psoriasis. However, biologic medications come at a significant cost. Due to the complex and costly development and minimal competition, treating one patient with biologic therapy can cost in excess of hundreds of thousands of dollars per year. In 2019, biologics accounted for $211 billion of United States prescription drug spending or 43% of the total spend. The Biologics Price Competition and Innovation Act (BPCI Act) of 2009 created the biosimilar class of drugs as a way of creating competition for commonly used biologics following loss of patent protection and market exclusivity. As the name implies, biosimilars are legitimate copies of approved biologic medications that are no longer protected by patent. The FDA defines biosimilars as rigorously evaluated and tested biologic products that are highly similar with no clinically meaningful differences to their reference product. Biosimilars have the potential to increase competition in the market thus lowering costs for patients and plan sponsors, while also facilitating patient access.

The BPCI Act created an abbreviated but thorough regulatory pathway for the United States Food and Drug Administration (FDA) to approve a biosimilar medication. The manufacturer is required to establish that the biosimilar product is highly similar to a previously approved originator biologic reference product without any clinically meaningful differences in safety, purity, and potency. Biologics are large, complex molecules that are produced through a living organism, which introduces variations throughout the lifecycle of the biologic. Biosimilars are made by reverse engineering the original reference product. Complex protein structures of biologics cannot be perfectly duplicated because they are manufactured using different cell lines under different development conditions. Therefore, the testing includes a greater emphasis on analytical studies to demonstrate similarity with the biological reference product. As a result, the differences between approved biosimilars and reference biologics are comparable to differences between batches of the reference product. In addition, the regulatory pathway for development does not require biosimilars be studied in every condition for which the reference product is approved. Some biosimilar agents will not have all the same indications that the branded product has. Biosimilar indications will be extrapolated using extensive characterization that shows a biosimilar is like its reference product and will behave like the reference product for the conditions where the reference product has been approved. Generally, the difference in approved indications has not deterred the use of biosimilars across the range of approved indications due to the clinical similarities between the biosimilar and the reference product.

Biosimilars are relatively new to the marketplace. The FDA approved the first biosimilar in 2015, filgrastim-sndz (Zarxio®, Sandoz). The number of approved biosimilars has increased steadily each year. To date, there have been 38 approvals and 22 biosimilar product launches. There are over 100 additional biosimilars in development with expansions into new therapeutic areas including growth hormone, infertility, bone health, and immunosuppressants. While a relatively small number of biosimilars are available in the market, the largest revenue biologic drugs in the United States have yet to face competition. The patents for 17 major biologics are set to expire over the next decade and the potential to save over $200 billion in specialty drug spend by 2031.

Both generics and biosimilars offer more affordable medication options. However, there is a significant fundamental difference in two products created. Identical generic versions of small molecule medications can be chemically synthesized in a simplistic process. On the other hand, biosimilars cannot be identical to their reference product due to their size and complexity. As a result, the processes used

to develop generic medicines cannot be applied to the development of biosimilar medicines. They require a more extensive FDA approval process. In 2019, the FDA published guidelines that manufacturers must follow in order for a biosimilar agent to be deemed interchangeable, or substitutable by the dispensing pharmacist with the reference product without prescriber authorization. A biosimilar is considered interchangeable if the manufacturer submits additional information to the FDA that demonstrates the biosimilar can be expected to produce the same result as the reference product in any given patient. In addition, the FDA requires that patients can switch back and forth between the interchangeable biosimilar and the reference product with no safety risk or decreased effectiveness. Semglee® (insulin glargine-yfgn) became the first interchangeable biosimilar for its reference product, Lantus® (insulin glargine), in July 2021. A biosimilar for Humira®, Cyltezo (adalimumab-adbm), was the second biosimilar to receive an interchangeable designation for a single strength of Humira in October 2021. In August of this year, Cimerli (ranibizumab-eqrn) became the third approved interchangeable biosimilar and first ophthalmic product to receive the designation. It is expected to launch in October. It should be noted that an interchangeable biosimilar is not better or safer than a biosimilar without the designation. The clinical safety and effectiveness are the same. Interchangeability only impacts the requirements for pharmacists before dispensing a biosimilar to a patient.

More and more biosimilar products are expected to be granted interchangeability. It has yet to be determined how important this designation is to patients and prescribers, but this should provide enhanced ability for pharmacies to provide cost saving options to patients and payers as compared to the referenced product, similar to traditional generic products. Humira is the highest-grossing medication in the world and the pending patent expiration will be the largest financial loss-of-exclusivity event for drug products. To date, the FDA has approved seven biosimilars for Humira and as many as 12 may enter the market in 2023. Amjevita was the first adalimumab biosimilar approved in 2016 and is expected to launch first in January 2023 but will not be considered interchangeable. Cyltezo is expected to launch in July 2023 with the interchangeable designation. If the market dynamics seem to give an advantage to competitors who hold the interchangeable designation, more manufacturers may spend the extra money and time to conduct additional studies to submit to the FDA. That will open the door to leveraging the competition between individual biosimilars and between the Humira and its biosimilars, a scenario that will be repeated with other biologics as more biosimilars reach the market.

With the pending launch of biosimilars for Humira in 2023, there will be a tremendous focus on these agents to provide cost savings. Several characteristics of the adalimumab biosimilars will influence utilization including timing of market availability, low versus high concentration, citrate free formulations, latex-free delivery systems, interchangeability designation and smaller needle gauge. Table 1 provides a snapshot of the upcoming Humira biosimilar landscape:

Table 1. Upcoming Adalimumab Biosimilar Products

Product (Manufacturer)	FDA Approved	Estimated Launch	Seeking Interchangeability	Concentration	Citrate Free	Latex Free	Needle Size
Amjevita (Amgen)	Yes	1/31/23	Unclear	Low (50mg)	Yes	No	29G Syr./ 27G Pen
Hadlima (Samsung/ Organon)	Yes	6/30/23	Yes	Low (50mg)	No	Yes	29G Syr./ 29G Pen
Hadlima HC (Samsung/ Organon)	Yes	7/1/23	Yes (expected post-launch)	High (100mg)	Yes	Yes	29G Syr./ 29G Pen

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Cyltezo (Boehringer Ingelheim)	Yes	7/1/23	Yes (approved)	Low (50mg)	Yes	No	27G Syr./ 27G Pen
AVT-02 (Teva)	No - expected 12/2022	7/1/23	Yes (FDA considering application for approval and interchangeability at the same time)	High (100mg)	Yes	Yes	Unknown
Yusimry (Coherus)	Yes	7/1/23	No	Low (50mg)	Yes	Yes	Unknown
Yuflyma (Celltrion)	No – expected late 2022	7/1/23	Yes	High (100mg)	Yes	Yes	29G Syr./ 29G Pen
SB5-HC (Organon)	No	7/1/23	Yes	High (100mg)	Yes	Yes	29G Syr/29G Pen
Hulio (Viatris/ Mylan)	Yes	7/31/23	No	Low (50mg)	Yes	Yes	29G Syr./ 29G Pen
Abrilada (Pfizer)	Yes	7/1/23	Yes (application under review)	Low (50mg)	Yes	Yes	29G Syr./ 29G Pen
Hyrimoz (Sandoz)	Yes	9/30/23	No	Low (50mg)	No	No	27G Syr./ 27G Pen
Idacio (Fresenius Kabi)	No – expected 4Q22	9/30/23	No	Low (50mg)	No	Yes	29G Syr./ 29G Pen
Hyrimoz HCF (Sandoz)	No – expected 3/23	4Q23	Unknown	High (100mg)	Yes	Unknown	Unknown
ABP-501 HC/ Amjevita HC (Amgen)	No	2024 or after	Yes	High (100mg)	Yes	No	29G Syr./ 27G Pen
Yusimry HC (Coherus)	No	TBD	Unknown	High (100mg)	Unknown	Unknown	Unknown

Some key market factors will also influence the adoption of adalimumab biosimilars. Initially, there will only be one biosimilar, Amjevita, that will be available in January 2023 due to the settlement agreements. However, uptake may be somewhat low due to an anticipated minimal discount to Humira and the availability of only the low concentration strength. Although high-concentration and low-concentration versions of Humira are available on the market today, approximately 85% of the current Humira utilization is for the higher concentration product (i.e., 100mg/ml). Currently, Humira and Hadlima are the only current adalimumab products that have a high-concentration formulation approved by the FDA, but it is anticipated that by the time Hadlima will be market available, at least 3 other high concentration products will be available, increasing the number of competitors. Another important factor to consider is whether a product is free of citrate. Citrate-free formulations allow for patients to experience less injection site pain as will the use of a smaller needle during adalimumab administration. Out of all the adalimumab products approved or being considered by the FDA, only Hyrimoz and the low-concentration version of Hadlima will *not* have a citrate-free option when they enter the market. Initially, Hadlima HCF (Organon), ATV-02 (Teva), and Yuflyma (Celltrion) may have a market advantage. All 3 products will be the high concentration strength, likely interchangeable at launch or shortly after, as well as citrate and latex free.

In addition to these market factors, one of the major determinants of adoption of biosimilar adalimumab will be the cost. Pricing for these biosimilars is not yet available, but due to the large number of products available, it is anticipated to be a competitive market, both from a list price and available rebates. Having multiple competitors for adalimumab should provide cost savings likely beginning in the third quarter of 2023.

As with biologics, coverage of biosimilars under the pharmacy or medical benefit is largely driven by route of administration. Biologics that are infused or injected in the provider's office or in an inpatient setting are usually covered under the medical benefit for commercial insurers. This would include many biologics and biosimilars for oncology as well as the new ophthalmic ranibuzumab biosimilar for age-related macular degeneration. Conversely, products that can be self-administered by the patient or caregivers are typically covered under the pharmacy benefit. Pharmacy benefit managers (PBMs) will drive preferred product choice for biosimilars based on available clinical and safety information and the pricing discounts available. PBMs may also suggest the implementation of step therapy programs to encourage the use of preferred biosimilars initially, especially in new-start patients. Ideally, payers would consider structuring the pharmacy benefit to encourage patients to choose the lower cost agents and biosimilars when they are available. Lowering member out-of-pocket costs for biosimilars should promote adoption of the biosimilars and help drive down overall healthcare costs. However, a high proportion of costly medications today are subject to manufacturers' copay cards which minimize patient out-of-pocket costs, at least for the first year of therapy.

A recent Evernorth analysis estimates that biosimilar competition can save the United States $225 billion to $375 billion in pharmacy spend by the year 2031. While the financial benefits of increasing biosimilar use are significant, many factors may impact their adoption. A large educational effort is a key component to assist in capitalizing on the cost savings potential of increased biosimilar utilization. Prescribers and pharmacists need to be educated on what biosimilars are available, the regulatory approval process, their clinical safety and efficacy, as well as the cost savings they can provide to patients and payers. Likewise, patients need to understand that biosimilars are safe and clinically effective products that may reduce their out-of-pocket costs and increase their access to therapy. Education coupled with financial incentives, should improve biosimilar uptake thus helping to reduce the financial burden associated with soaring healthcare costs.

References

1. https://www.iqvia.com/insights/the-iqvia-institute/reports/biosimilars-in-the-united-states-2020-2024
2. https://www.centerforbiosimilars.com/view/specialty-biologics-report-predicts-rise-in-biosimilar-access
3. https://www.evernorth.com/articles/the-coming-wave-of-biosimilar-medications
4. https://uspharmacist.com/article/what-is-the-future-of-cost-savings-with-biosimilar-drugs
5. https://www.specialtypharmacycontinuum.com/Policy/Article/08-22/Magellan-Rx-Reports-Millions-in-Savings-From-Onc-Biosimilars/67791

6. https://newsroom.cigna.com/biosimilar-medication-lower-drug-prices
7. https://www.pfizerbiosimilars.com/biosimilars-regulatory-considerations
8. https://www.managedhealthcareexecutive.com/view/are-interchangeable-biosimilars-better-
9. https://www.healio.com/news/rheumatology/20220107/cyltezo-paid-the-price-for-interchangeable-biosimilar-approval-will-it-be-worth-it
10. https://www.cardinalhealth.com/en/product-solutions/pharmaceutical-products/biosimilars/humira-biosimilar-landscape-overview.html
11. https://biosimilarsrr.com/2022/07/13/self-injectable-biosimilar-drugs-and-the-pharmacy-benefit/
12. https://www.zs.com/insights/pharmacy-benefit-is-a-whole-new-ball-game-for-biosimilars