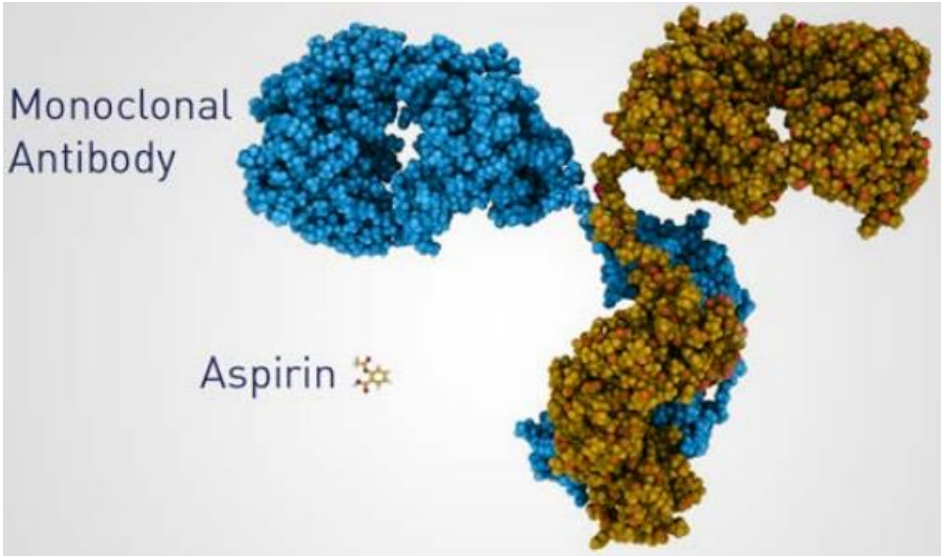
New Alternatives for Branded Biologics

We've all heard about generic drugs. They are time tested and battle proven medicines that are more affordable than their patented predecessors. These branded drugs consistently break new records for high treatment costs while overall drug prices have increased faster than inflation for decades. The prices can be scary. For example Alexion's Soliris is estimated to cost up to $600,000 per year and BioMarin's Brineura at an incrementally higher $700,000 for a year of treatment.[1] The availability of non-branded copies provide hope that prices will be affordable for all stakeholders in the system. In recent decades biologics have emerged on the scene from only a small proportion of drug spending in the 1990s to 43% of total drug spending in 2019.[2] Biologics are much larger molecules and more complex than the aspirin and statin tablets of yesteryear. Not only are they different from these small molecule drugs but they fall under a different approval regime both for new biologic entities and biosimilars.

Since the turn of the millennium, biologics have emerged as one of the most important drug classes and in 2020, five of the top ten drugs by revenue were biologics.[3] Biologics have also broken price records with many therapies running in the hundreds of thousands of dollars per course of treatment and some even above $1 million.[4] This class of medicine merits a higher price tag as materials, manufacturing processes and research and development costs for biologics are greater compared with small molecule drugs. However, one of the primary reasons biologics are so expensive is that they have few competitors. In contrast to generic small molecule drugs, it is very difficult to produce an equivalent of a biologic as they are very complex and it is challenging to determine their composition.

Exhibit I - Size and Complexity of Proteins[5]



[1] Source: Specialty Drugs: 10 of the Most Expensive. Leigh Ann Anderson, October 20, 2019.
[2] Source: IQVIA. Biosimilars in the United States 2020-2024.
[3] These biologics are Humira, Keytruda, Eylea, Stelara and Opdivo.
[4] Zolgensma for example as explained in an article here: At $2.1 Million, New Gene Therapy Is The Most Expensive Drug Ever.
[5] Source: Biological Product Definitions. US Food and Drug Administration, Accessed September 2021.

Biologics and Biosimilars

A biologic, biological drug or biological medical product is manufactured from living cells and includes such broad medicines as antibodies, interleukins, vaccines and insulin among others. The primary cells used to produce the biologics are varied and include mammalian, fungal, plant and bacterial expression systems. A genetic sequence is inserted in these cells which is then placed in bioreactors under very specific nutrient, temperature, pH, agitation and pressure to generate the desired biologic output. The molecular structure of a biologic is complex and not precisely known. This class of drug has emerged in many cases as the most effective means to treat a variety of medical illnesses and conditions where no other treatments exist.

Traditional drugs are governed by the Food, Drug, and Cosmetic Act, the law that originally created the Food and Drug Administration (FDA). Biologic medicines are governed by a different law, the Public Health Service Act and require that a Biologics License Application be submitted prior to FDA approval in the United States.

A biosimilar is a biologic with no clinically meaningful differences from an approved biologic reference product. Aspects of the biosimilar, including structure, function, purity, chemical identity and bioactivity are compared with the approved biologic. If the molecules are sufficiently similar then the copy is considered a biosimilar and can be evaluated by the FDA for approval as a biosimilar or interchangeable biosimilar with the reference product.

While the concept of biosimilars is comparable to generics, there are important differences. Generic copies of branded drugs are exact chemical replicas that match the originator product in terms of dosage form, safety, strength, route of administration, quality and performance. Biosimilars are manufactured by living organisms and are not exact replicas of their reference product due to their complexity. Their structure and composition are instead highly similar and defined by the expression system and conditions under which they were manufactured. In fact, many approved biologics do not even match the composition of the original FDA approved product.[6] Additionally, the FDA and EMA require supplemental studies in animals and humans for biologics, which is not needed for generics. An article in U.S. Pharmacist provides a detailed comparison that the reader can reference.[7] These drugs are similar to their reference biologics and only have differences that are not clinically meaningful.

Financial Impact

A statistic frequently cited by the FDA points out that biologics are two percent of prescription volume but 37% of total prescription drug spend. An IQUVA report[8] estimated that biologics accounted for $211 billion in US prescription drug spending in 2019 and a 2020 summary of highest revenue generating drugs finds that five of the top eight are biologics.[9] This dramatic growth and financial incentive has prompted many biopharmaceutical companies to develop biosimilars.

Legislation to Navigate the Way

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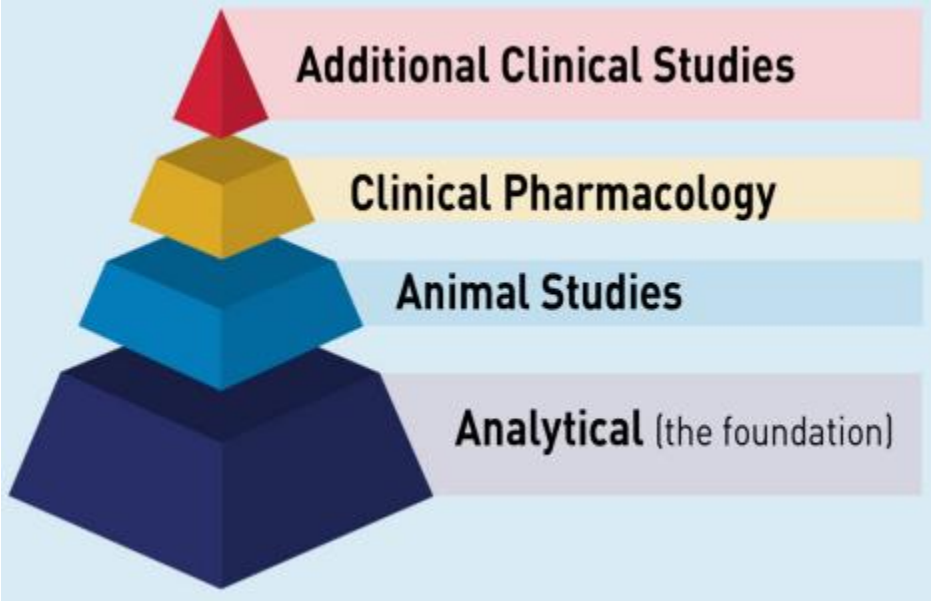
[6] Mehr, S., Zimmerman, M. Is a Biologic Produced 15 Years Ago a Biosimilar of Itself Today? American Health Drug Benefits. 2016 Dec; 9(9): 515–518.
[7] Biosimilars: Not Simply Generics. U.S. Pharmacist, June 18, 2019. Celia Lu and Elsen Jacob.
[8] Source: IQVIA. Biosimilars in the United States 2020-2024.
[9] Pharmaceutical Technology. The Top Selling Prescription Drugs by Revenue. January 27, 2020.

During the negotiation of the Affordable Care Act, the US Congress enacted the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The BPCI created an approval pathway for biologic drugs which allowed those with expired exclusivity and patents to be classified as either biosimilar to or interchangeable with FDA licensed reference biological products. The Act addresses many areas including the approval process, patent resolution and exclusivity. The approval process for a biosimilar is substantially more involved than what is required for approval of a generic; however, it is an abbreviated procedure that substantially relies on studies conducted by the innovator. Patent resolution allows for expedited litigation of expired patents and requires information exchange between the biosimilar applicant and the branded company. Exclusivity terms were also addressed in the Act and in the United States, innovators are granted 12 years of data exclusivity from the product's original approval date.

Biosimilar Approval Process in the United States

Biosimilars and interchangeable products are governed by Public Health Act Section 351(k) which guides the approval process. Under the 351(k) Act, marketing clearance for a biosimilar may not take place until 12 years after the approval date for the reference product. In contrast to generic drugs which must show chemical equivalence to the original product, biosimilars must provide supportive data from analytical, nonclinical and clinical studies to support similarity with the reference product.

Exhibit II – Biosimilars Evidence Development[10]



The FDA has created a stepwise approach to support approval of a biosimilar. The base of the application is built on the analytical assessment. This section examines the manufacturing process, characterizes reference product quality characteristics and product variability. Some details considered include the expression system, receptor binding and immunochemical properties, impurities, finished

[10] Source: US Food & Drug Administration Presentation. Overview of the Regulatory Framework and FDA's Guidance for the Development and Approval of Biosimilar and Interchangeable Products in the US.

drug product and stability. These characteristics are selected based on the nature of the biologic, its structure and heterogeneity of the reference product and proposed biosimilar.

Animal studies are important to clarify product toxicity prior to commencing clinical work. The extent of the toxicity studies will depend on available information related to the similarities and differences between the reference and proposed product. Pharmacokinetic (PK) and pharmacodynamic (PD) work may provide additional clarity in the animal model.

Results from analytical and animal studies determine the nature and scope of the clinical studies. At least one clinical study that compares the immunogenicity of the proposed and reference products is necessary. If questions remain, a comparative study is required to support biosimilarity that will be built on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment.

Barriers to Biosimilars

Despite the legislation that was put into place in both the United States and the EU, biosimilars have not flourished as was hoped. There are 31 approved biosimilars for 11 reference products approved in the US[11] and 78 biosimilars for 18 reference products in the EU.[12] The reference product sponsors erect many barriers including follow-on patents to prevent competition despite some biologics receiving protection well beyond the original term of patent protection. Late stage patents that address minor features of the biologic are sought after commercialization is underway. Another hurdle is contracting practices that grant discounts and rebates to pharmacy benefit managers and formularies to exclusively distribute one biopharmaceutical's portfolio of products. If a branded drug is switched out for a biosimilar, discounts in excess of the savings from the biosimilar switch can be lost. A third approach to limit uptake of biosimilars is called counter-detailing where sales representatives visit with providers and raise doubts about the safety and efficacy of biosimilars. Other obstacles include state laws, FDA requirements and lack of information and education also hinder greater use of biosimilars.

Biosimilar Action Plan

Expectations were high that biosimilars would flourish following the BPCI Act. However, due to several of the barriers we mention above, only a few biosimilars were approved in the years following the legislation. In response, stakeholders responded including FDA Commissioner Dr. Scott Gottlieb who promoted the Biosimilar Action Plan in mid-2018 to improve the efficiency of the biosimilar and interchangeable development and approval process. In remarks that were made in conjunction with the release, Dr. Gottlieb noted that biologics made up 70% of the growth in drug spending over the five years ending in 2015 and that they represented 40% of the total spending on prescription drugs even though less than 2% of Americans used them.[13]

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[11] As of September 17, 2021. Drugs.com.

[12] How the US Compares to Europe on Biosimilar Approvals and Products in the Pipeline. Aydin H. Harston, March 8, 2021. biosimilarsip.com

[13] Remarks from FDA Commissioner Scott Gottlieb, M.D., as prepared for delivery at the Brookings Institution on the release of the FDA's Biosimilars Action Plan. July 18, 2018.

The document sought to increase scientific and regulatory clarity and better the understanding by payors, patients and providers of the potential for biosimilars. The document also attempted to reduce the incidence of innovators delaying competition to maintain protection longer than intended.

In the calendar year after the implementation of the plan, the number of biosimilars approved increased from five in 2017 to ten in 2019. Worldwide sales of biosimilars were estimated at $2.6 billion in 2017 and expected to rise to $11.7 billion in 2021[14] demonstrating a material uptake in acceptance for the class.

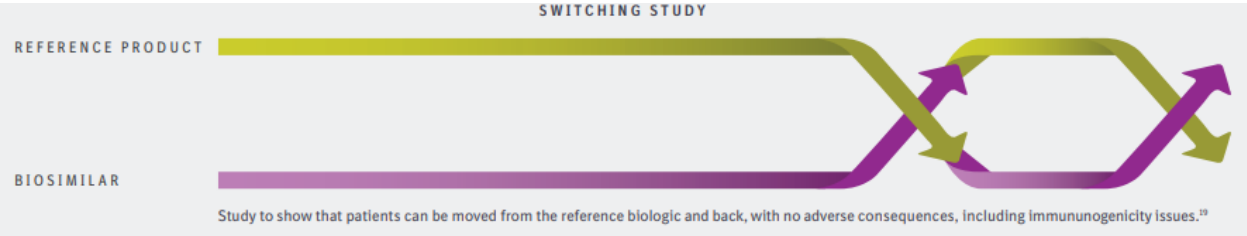
Further work by the Biden administration is seeking to reduce prescription drug prices overall and in September 2021, Health and Human Services announced a proposal to reduce costs to consumers through competition, innovation, and transparency. The administration's efforts are also pushing to accelerate entry of biosimilars into the market and shortening the period of exclusivity.[15]

Biosimilar Interchangeability

FDA approval of a generic drug is sufficient for it to be considered interchangeable with its small molecule reference product. However, in the biologics universe, a second step after a drug is approved as a biosimilar is required to support its interchangeability with its reference product in the United States. A copy of a biologic can be approved at two different levels. It can be a biosimilar, which may not be substituted for the reference product without the prescriber's consent or it can be an interchangeable biosimilar, which can be substituted without the intervention of the prescriber.

Additional work is required to be approved as an interchangeable biosimilar in the United States including a switching study that shows that there is no impact on efficacy when the products are switched. When a product is designated as interchangeable, state laws will govern whether or not pharmacies can or must switch one product for another.

Exhibit III – Switching Study Design[16]



The first interchangeable in the United States was approved in June 2021. Viatris' (NASDAQ: VTRS) insulin glargine-yfgn (Semglee) for treatment of diabetes was granted interchangeable status by the FDA. The product will be available before the end of the year and Semglee will be granted 12 months of

[14] Source: Evaluate Pharma, Ltd. Worldwide Rx sales based on consensus broker forecasts of biosimilar products. At this time brokers are not forecasting sales for a large number of biosimilars. As a result the worldwide market is currently forecast to be much smaller than its potential.

[15] Biden Administration's Drug Pricing Plan Calls for Bold Action by Congress. National Law Review. September 13, 2021

[16] Source: Boehringer Ingelheim. From the Lab to the World.

exclusivity. There are multiple names to refer to the different iterations of the biologic which we clarify in the exhibit below.

Exhibit IV – Biologics Names, Branded and Biosimilar

	Reference Product	Biosimilar Interchangeable
Brand Name (Sanofi)	Lantus	Semglee
Biosimilar Name (Viatris)	insulin glargine	insulin glargine-yfgn

The interchangeable designation will allow pharmacies to switch the biosimilar for the reference product when a product is prescribed. State law supersedes this sanction; however, most states allow the substitution of an interchangeable product as long as provider and sometimes patient are notified. A few states even require that a generic version be substituted for a brand version if it is cheaper.

Boehringer Ingelheim's Cyltezo

Abbvie's Humira also known as adalimumab has been one of the highest revenue biopharmaceutical and biologic products in the world. With sales of over $20 billion[17] per year in 2020, this TNF-α inhibitor surges past other well-known biologics such as Rituxan and Enbrel that have less than half of the revenues. The product is approved in twelve different indications including Crohn's disease, rheumatoid arthritis, psoriasis and ulcerative colitis among others. Despite being approved in 2002, Humira has maintained its intellectual property protection for almost two decades and successfully fended off competitors. The revenue opportunity has attracted others to the space in an effort to bring down the price for this critical biologic. One of the responses has been Boehringer Ingelheim's Cyltezo® (adalimumab-adbm).

Boehringer conducted its VOLTAIRE-X Phase III clinical trial to obtain a biosimilar and interchangeable designation for its version of adalimumab. The trial examined the effect of switching between Humira and Cyltezo in patients with plaque psoriasis. Cyltezo was approved in August 2017 as a biosimilar for the treatment of multiple chronic inflammatory diseases; however, in a 2019 settlement with AbbVie, it will not be available for sale until July 2023. On October 15, the company announced that the FDA had granted its supplemental Biologics License Application (sBLA) for Cyltezo as the first interchangeable biosimilar with Humira. This latest approval designates it as Interchangeable across all of Humira's indications.

The mission to develop a robust and thriving biosimilars market is underway, although it has taken many years or hard work by companies, consumer advocates and the FDA to get here. When generics were first approved, it took decades for them to be accepted but they now comprise 9 out of 10 prescriptions filled.[18] Perhaps Cyltezo can contribute to the same milestone for biosimilars.

In Conclusion

[17] Source: Evaluate Pharma Ltd.
[18] Generic Drugs. FDA website, February 5, 2021.

With the precedent set by the Hatch-Waxman Act in 1984 with generics of small molecule drugs, the hope is that the same price benefits can be brought to the biologics market from 2009's BPCI Act and follow on legislation. While biosimilars have had a slow start due to significant barriers, stakeholders such as the FDA, biopharma companies, providers and patient groups have pushed forward to simplify the approval process, increase prescriber confidence in biosimilars and reduce efforts by patent holders to block new options for patients. One of the strongest responses to this unmet need has been Boehringer Ingelheim's pursuit of a biosimilar for Humira which was approved by the FDA on October 18th, 2021 as an interchangeable biosimilar. Biosimilars promise to bring critical medicines to patients that need them for health and quality of life at a cost that is affordable and sustainable.

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