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Cordavis: Bringing to Life the Promise of High-Quality Biosimilars

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The history of pharmaceuticals is a path grounded in research and scientific progress. The development of biosimilars marks an important milestone in this journey, creating the potential to treat cancers and other chronic conditions at a more affordable price point than biologics. With the right oversight and production considerations, biosimilars can boost access to care, control costs and improve health outcomes.

Background:

What is a biologic? Biologic therapeutics represent a relatively new category of pharmaceuticals that are derived from living cells such as bacteria, yeast, or mammalian cultures. Unlike traditional small molecule drugs synthesized from chemicals, biologics are complex proteins and molecules manufactured using advanced biotechnology processes. These innovative therapeutics represent one of the fastest-growing types of medications in the United States providing targeted treatment options for cancers, autoimmune diseases, and other serious conditions.

The size of the market: The global market for biologics was estimated to be $382B in 2022, and by 2027, the total spend is projected to be close to $1.5T.[i] The U.S. biologics market is estimated to have grown 12.5% annually on average over the last five years and now comprises 46% of total drug spend.[ii] Despite their outsized share of total drug cost, only about 1-3% of a patient population are treated by biologics, a statistic that highlights the high cost yet focused use of these medications.

The promise of biosimilars: In light of the increasing cost attributed to biologics, biosimilar drugs have been heralded as a substantial cost savings opportunity, reminiscent of the generic drug wave a decade ago.[iii] According to the Food & Drug Administration (FDA), a biosimilar is a "biological product that is highly similar and has no clinically meaningful differences from an existing FDA-approved reference product." In fact, it is estimated in the coming years, biosimilars are projected by some experts to yield $133 billion in savings to the US health care system.[iv]

One key piece of legislation that catalyzed the advent of biosimilars was the Biologics Price Competition and Innovation Act (BPCIA) enacted in March of 2010.[v] The goal of the BPCIA is to provide a mechanism for biosimilar drug candidates to go through an abbreviated approval process. This law encouraged competition and innovation for the development of biosimilars.[vi] The first biosimilar drug to receive FDA approval was filgrastim-sndz, a biosimilar to Neupogen on March 6, 2015.[vii,viii]

The biosimilar approval process: Under the Biologics Price Competition and Innovation Act of 2009 (BPCIA), manufacturers can rely on prior scientific data and evidence about the reference product's safety and efficacy rather than conducting costly redundant clinical trials. However, the FDA still requires substantial evidence demonstrating "biosimilarity" and meeting rigorous standards. Specifically, biosimilar applications must prove the candidate has the same mechanisms of action, administration route, dosage form, and strength as the reference product. Moreover, biosimilar manufacturers can only seek approval for indications already granted to the originator biologic.

Additionally, manufacturing facilities must adhere to the FDA's stringent current Good Manufacturing Practices which oftentimes requires a pre-approval onsite inspection. This tailored regulatory framework strikes a balance between enabling more cost-effective biosimilar development while still requiring robust comparability data to ensure safety and efficacy for patients. As of January 2024, there have been a total of 45 biosimilars approved by the FDA in the U.S. These biosimilars span across therapeutic areas including oncology, immunology, hematology and ophthalmology.[ix,x]

The Complexity of Manufacturing Biosimilars:

As mentioned above, biologics have inherent minor variability in their structure, which makes them difficult to be replicated. Thus while the biologic drug cannot be exactly copied, the biosimilar development process focuses on the attributes that matter the most (critical quality attributes or CQAs), specifically those that have clinical impact and confer therapeutic value. Succinctly put, a robust biosimilar manufacturing process must match the CQAs of the originator product as closely as possible.[xi]

Demonstrating similarity: A manufacturer developing a proposed biosimilar must prove that their candidate is highly similar to the reference product through extensive comparability analysis. This includes analyzing the function and the structure of the proposed biosimilar and the reference product across many structural, chemical, biological and pharmacological CQAs, before establishing equivalence in clinical efficacy and safety.[xii, xiii] The process of developing a biosimilar is complex and highly regulated, requiring deep scientific expertise and advanced analytical capabilities. Unlike generic small-molecule drugs, biosimilars cannot be identical copies of the original biologic drug.

Managing the production: The conditions under which the biosimilar producer cells are cultured are also critical. Variables like temperature, pH, and nutrient levels must be precisely controlled to mirror the original process. Even modest deviations can alter the structure and function of the resulting protein. Cell culture expertise and stringent quality control are essential to ensure optimal biosimilar production.

Demonstrating similarity: Once manufactured, rigorous comparative testing verifies that the biosimilar engages the same biological targets and pathways as the original drug. Binding affinity, potency, and other functional attributes are evaluated using sensitive bioassays. This requires in-depth knowledge of the biologic's mechanism of action to detect potentially meaningful differences from the original.

Ensuring stability: Developing the formulation is another key step, providing a stable delivery system that maintains the drug's integrity. Excipients must be selected to prevent degradation during storage and transport. The goal is a formulation that delivers the active drug reliably and predictably over time.

Generating evidence: Finally, clinical trials must demonstrate the biosimilar's safety and efficacy in patients. While biosimilars are not required to independently prove efficacy, studies must show no clinically significant differences compared to the original biologic. Sophisticated trial designs and statistical analysis are used to enable sensitive detection of variations before approval.

The challenging path to market access and adoption: The level of sophistication and expertise in the biosimilar development process requires more time and resources than developing a small molecule generic drug. It is estimated that the initial investment and time required to bring a biosimilar to market ranges from 5–10 years and an investment of $100-250 million. Conventional generic drugs, on the other hand, generally require about two years and $1-10 million to commercialize.[xiv] This enables generic manufacturers to be able to enter and exit markets fairly easily, depending on specific market dynamics.

Compounding these challenges is the uncertainty surrounding market demand for biosimilars. Despite their potential to offer less costly alternatives to biologics, biosimilars face hurdles in market acceptance due to physician and patient confidence in their efficacy and safety. Biosimilar adoption also must overcome various legal and competitive strategies employed by originator companies and varying global regulatory pathways for interchangeability and substitution. This demand uncertainty can jeopardize the long-term viability of the biosimilar market, as manufacturers weigh the high upfront costs and complex production demands against unpredictable market adoption and return on investment.

The biosimilar marketplace faces additional complexity due to the large number of entrants with varying expertise. As of 2020, only 13% of biosimilars in development were from six major pharmaceutical companies. The vast majority were being developed by over 40 smaller companies, many with limited experience in biologics or biosimilars.[xv] Indeed, while the process for biosimilar approval ensure they have met the highest standards for the drug substance, each manufacturer still has variability in many other choices that can cause supply disruptions for providers and patients, including supply, pricing, patient support and physician education. This fragmentation raises concerns about whether manufacturers can generate and maintain sufficient high-quality supply for global markets over the long term.

CVS Health's Role

CVS Health is deeply committed to driving the adoption of low-cost, high-quality medicines. From establishing Red Oak for generic drug sourcing to leading the charge as the first pharmacy benefits manager to include a biosimilar on our formulary, CVS Health has embraced innovative approaches to promoting the adoption of generic and biosimilar drugs. The recent launch of Cordavis marks a new chapter in CVS Health's commitment to expanding access to medicines. Cordavis™, a CVS Healthspire™ company, was founded in 2023 and charged with partnering with select manufacturers to co-manufacture and commercialize high value biosimilar products for the U.S. pharmaceutical market. Through multi-year contracts and robust quality oversight, Cordavis aims to ensure stable and predictable demand, promoting an economically viable biosimilar marketplace for years to come.

The loss of market exclusivity of Abbvie's Humira in January 2023 afforded Cordavis the opportunity to launch its own low-cost adalimumab biosimilar. After a rigorous vetting process, Cordavis partnered with Sandoz to co-manufacture and commercialize Hyrimoz. At launch, the list price of the Cordavis Hyrimoz was more than 80% lower than the current list price of Humira, further accelerating the adoption of biosimilars for this important drug class.

As a co-manufacturer, Cordavis will work with biosimilar developers that are best able to consistently supply quality product at a competitive price. Given the complexities of these products, Cordavis has extensive quality management practices in place. Cordavis utilizes a rigorous vetting and oversight process to ensure the quality, safety, and reliability of its co-manufactured biosimilar products. When evaluating potential partner manufacturers, Cordavis undertakes a thorough assessment across multiple dimensions, including quality systems, clinical quality and safety of the manufacturers' biosimilar portfolio, corporate behavior and reputation, regulatory track record, and operational capabilities. Additionally, Cordavis, supported by the CVS Health Medical Affairs team, specifically reviews the clinical data, formulation, delivery system, and real-world evidence for the potential product to fully understand its benefit and value for patients.

Once a co-manufacturer is selected, Cordavis has in-process quality oversight which includes the development of demand forecasts and close collaboration of production planning and scheduling to

ensure adequate supply for projected patient needs. The team reviews and approves procurement plans for necessary raw materials as well as periodically analyzing inventory reports from the manufacturer. Oversight continues through the manufacturing process with batch-by-batch review of critical quality documents including Certificates of Analysis and Compliance prior to release. The Cordavis team must approve any proposed changes to production specifications or subcontractors described in regulatory filings to maintain compliance.

To ensure continuous quality assurance, Cordavis performs periodic audits of co-manufacturer's facilities using a risk-based approach. Cordavis may also select batches for laboratory testing throughout the year at an approved lab, providing further verification of product quality attributes. Additionally, third-party inspections provide on-site assessment of manufacturing facilities and operations. In the event of a product related complaint, Cordavis participates in investigations and resolutions, putting patient safety first.

This comprehensive approach to oversight and collaboration with manufacturing partners gives Cordavis confidence in supplying high-quality, reliable biosimilar drugs to improve patient access and outcomes. Cordavis takes seriously its responsibility to ensure these products meet the highest quality and regulatory standards from start to finish and reaching resolutions on co-manufactured product-related complaints.

The advent of biosimilars promised to yield substantial cost savings and expand patient access to critical specialty medications. However, inherent manufacturing complexity, high development costs, and market uncertainty have posed challenges in establishing a thriving biosimilar marketplace. Cordavis is strategically positioned to help overcome these hurdles through co-manufacturing arrangements, rigorous quality oversight, and working with pharmacy benefits managers to offer formulary access. With extensive vetting processes, Cordavis selects only manufacturers with proven expertise and commitment to quality.

Ongoing oversight throughout the manufacturing lifecycle ensures adherence to exacting standards for safety, purity, and efficacy. Cordavis' launch of Hyrimoz biosimilar demonstrates the ability to accelerate biosimilar adoption and deliver cost savings to patients and payors. With clinical quality and patient safety as our north star at CVS Health, Cordavis addresses the core challenges facing biosimilars today. CVS Health remains steadfast in our mission to establish a thriving, sustainable biosimilar marketplace that expands access to these life-changing medications.

In Summary:

- **Biosimilars are complex and cost-effective alternatives to biologics:** Biosimilars are biological products that are highly similar and have no clinically meaningful differences from an existing FDA-approved reference product. They offer targeted treatment options for cancers, autoimmune diseases, and other serious conditions.
- **Biosimilar development is challenging and requires rigorous comparability analysis:** Biosimilars are not identical copies of the original biologic, as they are derived from living cells that have inherent variability. They must demonstrate similarity in structure, function, and clinical efficacy and safety to the reference product through advanced analytical techniques and clinical trials. The FDA ensures that biosimilars meet high standards of quality and manufacturing.

- **Biosimilar market faces uncertainty and fragmentation:** Despite the clinical standards set by the FDA and others as well as the potential savings and benefits of biosimilars, they face hurdles in market acceptance, legal and competitive barriers, and varying global regulatory pathways. The biosimilar market is also highly fragmented, with over 40 smaller companies developing biosimilars, raising concerns about their long-term viability and supply reliability.
- **CVS Health launches Cordavis to co-develop and commercialize biosimilars:** Cordavis is a CVS Healthspire™ company, that partners with select manufacturers to co-develop and commercialize high value biosimilar products for the U.S. market. Through multi-year contracts and quality oversight, Cordavis aims to ensure stable and predictable demand and promotes a sustainable biosimilar marketplace. Hyrimoz, a biosimilar to Humira, offers an 80% lower list price than the original biologic.
- **Cordavis has a comprehensive quality management process:** Cordavis selects only manufacturers with proven expertise and commitment to quality, and undertakes a thorough assessment of their quality systems, clinical data, regulatory track record, and operational capabilities. Cordavis also collaborates with them on demand forecasting, production planning, inventory management, and batch review. Cordavis performs periodic audits and testing of the co-manufactured biosimilars and participates in investigations and resolutions of product-related complaints.
- **Cordavis aims to expand access and affordability of biosimilars:** Cordavis addresses the core challenges facing biosimilars today, such as manufacturing complexity, high development costs, and market uncertainty. By co-developing and co-manufacturing high-quality, reliable biosimilars, Cordavis aims to accelerate their adoption and deliver cost savings to patients and payors. Cordavis also works with pharmacy benefits managers to offer formulary access and patient support. This mission is to establish a thriving, sustainable biosimilar marketplace that improves patient access and outcomes.

Appendix:

Table 1: FDA Approved Biosimilars[xvi]

Biosimilar Name	Approval Date	Reference Product
Avzivi (bevacizumab-tnjn)	December 2023	Avastin (bevacizumab)
Wezlana (ustekinumab-auub)	October 2023	Stelara (ustekinumab)
Tofidence (tocilizumab-bavi)	September 2023	Actemra (tocilizumab)
Tyruko (natalizumab-sztn)	August 2023	Tysabri (natalizumab)
Yuflyma (adalimumab-aaty)	May 2023	Humira (adalimumab)
Idacio (adalimumab-aacf)	December 2022	Humira (adalimumab)
Vegzelma (bevacizumab-adcd)	September 2022	Avastin (bevacizumab)
Stimufend (pegfilgrastim-fpgk)	September 2022	Neulasta (pegfilgrastim)
Cimerli (ranibizumab-eqrn)	August 2022	Lucentis (ranibizumab)
Fylnetra (pegfilgrastim-pbbk)	May 2022	Neulasta (pegfilgrastim)
Alymsys (bevacizumab-maly)	April 2022	Avastin (bevacizumab)
Releuko (filgrastim-ayow)	February 2022	Neupogen (filgrastim)
Yusimry (adalimumab-aqvh)	December 2021	Humira (adalimumab)
Rezvoglar (insulin glargine-aglr)	December 2021	Lantus (insulin glargine)
Byooviz (ranibizumab-nuna)	September 2021	Lucentis (ranibizumab)
Semglee (Insulin glargine-yfgn)	July 2021	Lantus (Insulin glargine)
Riabni (rituximab-arrx)	December 2020	Rituxan (rituximab)
Hulio (adalimumab-fkjp)	July 2020	Humira (adalimumab)
Nyvepria (pegfilgrastim-apgf)	June 2020	Neulasta (pegfilgrastim)
Avsola (infliximab-axxq)	December 2019	Remicade (infliximab)
Abrilada (adalimumab-afzb)	November 2019	Humira (adalimumab)
Ziextenzo (pegfilgrastim-bmez)	November 2019	Neulasta (pegfilgrastim)
Hadlima (adalimumab-bwwd)	July 2019	Humira (adalimumab)
Ruxience (rituximab-pvvr)	July 2019	Rituxan (rituximab)
Zirabev (bevacizumab-bvzr)	June 2019	Avastin (bevacizumab)
Kanjinti (trastuzumab-anns)	June 2019	Herceptin (trastuzumab)
Eticovo (etanercept-ykro)	April 2019	Enbrel (etanercept)
Trazimera (trastuzumab-qyyp)	March 2019	Herceptin (trastuzumab)
Ontruzant (trastuzumab-dttb)	January 2019	Herceptin (trastuzumab)
Herzuma (trastuzumab-pkrb)	December 2018	Herceptin (trastuzumab)
Truxima (rituximab-abbs)	November 2018	Rituxan (rituximab)
Udenyca (pegfilgrastim-cbqv)	November 2018	Neulasta (pegfilgrastim)
Hyrimoz (adalimumab-adaz)	October 2018	Humira (adalimumab)
Nivestym (filgrastim-aafi)	July 2018	Neupogen (filgrastim)
Fulphila (pegfilgrastim-jmdb)	June 2018	Neluasta (pegfilgrastim)
Retacrit (epoetin alfa-epbx)	May 2018	Epogen (epoetin-alfa)
Ixifi (infliximab-qbtx)	December 2017	Remicade (infliximab)
Ogivri (trastuzumab-dkst)	December 2017	Herceptin (trastuzumab)

Biosimilar Name	Approval Date	Reference Product
Mvasi (Bevacizumab-awwb)	September 2017	Avastin (bevacizumab)
Cyltezo (Adalimumab-adbm)	August 2017	Humira (adalimumab)
Renflexis (Infliximab-abda)	May 2017	Remicade (infliximab)
Amjevita (Adalimumab -atto)	September 2016	Humira (adalimumab)
Erelzi (Etanercept-szzs)	August 2016	Enbrel (etanercept)
Inflectra (Infliximab-dyyb)	April 2016	Remicade (infliximab)
Zarxio (Filgrastim-sndz)	March 2015	Neupogen (filgrastim)

As of December 11, 2023, there are 16 biosimilars pending FDA review.

Table 2: Biosimilar Candidates Pending FDA Review[xvii]

Biosimilar	Manufacturer	Brand Name & Designation	Innovator Product	FDA Filing Date
Adalimumab	Alvotech/ Teva	AVT02	Humira	19-Nov-20
Aflibercept	Biocon	MYL-1701P	Eylea	FDA 351(k) filing October 2021 (by Viatris)
Aflibercept	Formycon/Coherus Biosciences	FYB203	Eylea	FDA 351(k) filing June 29, 2023
Aflibercept	Celltrion	CT-P42	Eylea	FDA 351(k) filing June 30, 2023
Bevacizumab	Biocon	MYL-1402O	Avastin	March 2020
Denosumab	Sandoz	GP2411	Prolia/Xgeva	February 6, 2023
Eculizumab	Amgen	ABP 959	Soliris	February 2023
Insulin Glargine	Lannett	TBD	Lantus	N/A
Insulin Aspart	Biocon/Viatris	TBD	NovoLog	N/A
Tocilizumab	Fresenius Kabi	MSB11456	Actemra	August 1, 2022
Trastuzumab	Tanvex Biopharma	TBD	Herceptin	FDA application filed Oct 4, 2021
Trastuzumab	Prestige Biopharma	HD201	Herceptin	FDA application to be filed Q1-Q2 2023?
Trastuzumab	Sandoz/EirGenix	TBD	Herceptin	FDA application filed Dec 20, 2021
Ustekinumab	Alvotech/Teva	ATV04	Stelara	FDA application filed Jan 6, 2023
Ustekinumab	Celltrion	CT-P43	Stelara	FDA application filed June 2023
Ustekinumab	Formycon AB	FYB202	Stelara	November 30, 2023

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