BIOSIMILAR AND BIOLOGIC DRUGS

Biosimilar drugs are often confused with generic drugs. Both are marketed as cheaper versions of costly name-brand drugs. Both are available when drug companies' exclusive patents on expensive new drugs expire. And both are designed to have the same clinical effect as their pricier counterparts. But biosimilar drugs and generic drugs are very different, mainly because while generic drugs are identical to the original in chemical composition, biosimilar drugs are "highly similar," but close enough in duplication to accomplish the same therapeutic and clinical result. Another key difference is that generics are copies of synthetic drugs, while biosimilars are modeled after drugs that use living organisms as important ingredients. But many experts hope the two will share a critical commonality and that, like generics, biosimilars will dramatically lower the cost of biologic drugs.

Branded drugs are either synthetic, meaning they're made from a chemical process, or biological, meaning they're made from living sources. Synthetic branded drugs can be exactly replicated into more affordable generic versions, but because biologics involve large, complex molecules, they cannot. When drug manufacturers receive U.S. Food and Drug Administration (FDA) approval on a new drug, they obtain a patent ensuring that no other company can create or sell the drug for as long as the patent is in effect, generally 20 years. These exclusive patents allow for a monopoly on the drug, and, generally, an expensive price tag.

Biological products can include a wide range of products including:

- **vaccines**
- blood components
- gene therapy
- tissues
- proteins, like **monoclonal antibodies** and cell signaling proteins.

Unlike most chemically-derived small-molecule drugs, biological products are generally derived from a living organism, such as humans, animals, microorganisms or yeast. Clinically, they are used to treat patients with cancer, kidney diseases and autoimmune diseases, such as rheumatoid arthritis and Crohn's disease.

For example, **Enbrel** (etanercept) or **Humira** (adalimumab) are referred to as "large-molecule" drugs because they are larger and more complex in structure than small-molecule drugs. These products are very expensive, often in the tens-of-thousands of dollars per year, due to costs linked to complicated development and manufacturing. Often, patients will need to access these medications through a **specialty pharmacy**.

The Hatch-Waxman Act, passed in 1984, reduced the cost of synthetic branded drugs by allowing other companies to create generics, or identical but less expensive versions of the original, branded drug, once the patent expires. In 1984, generic drugs accounted for 19 percent of retail prescriptions. In 2016, they accounted for 89 percent, and a March report from the President's Cancer Panel found that the U.S. generic drug market saved the U.S. health care

system an estimated $253 billion overall in 2016, including $10 billion in savings for cancer drugs.

But at the same time as generic drugs have helped offset the high cost of name-brand medications, some newer drugs, such as the immunotherapy and targeted therapy drugs now commonly used to treat cancer, have driven up prescription prices even more. A May report from the IQVIA™ Institute from Human Data Science found that spending on cancer medications in the United States doubled from 2012 to 2017. Many of these newer-to-market drugs are biological drugs, or biologics, which are branded drugs made from living organisms like yeast, bacteria, or animal or plant cells. In 2005, biologics made up 39.1 percent of the $9.5 billion in Medicare drug spending. By 2014, they accounted for 62 percent of the $18.5 billion spent by Medicare on prescription drugs.

Now that the patents on high-priced biologics are beginning to expire, many experts hope that biosimilars, which are comparable but not chemically identical to their name-brand counterparts, may work the same way generics did to help offset drug prices. In 2010, Congress passed the Biologics Price Competition and Innovation Act, which established an abbreviated regulatory process for biosimilars and paved the way for their approval.

Biologics Vs Biosimilars

Biologics or biological products are medicines made from living organisms through highly complex manufacturing processes and must be handled and administered under carefully monitored conditions. Biologics include a wide variety of products such as gene and cell therapies, therapeutic proteins, monoclonal antibodies, and vaccines. Biologics are used to prevent, treat or cure a variety of diseases including cancer, chronic kidney disease, diabetes, cystic fibrosis, and autoimmune disorders.

A biosimilar is exactly what its name implies — it is a biologic that is "similar" to another biologic medicine (known as a reference product) which is already licensed by the U.S. Food and Drug Administration (FDA).

Biosimilars are highly similar to the reference product in terms of safety, purity and potency, but may have minor differences in clinically inactive components. In approving biosimilars, the FDA may require that manufacturers conduct a clinical study (or studies) sufficient to establish safety, purity or potency in one or more uses for which the reference product is licensed and the biosimilar seeks licensure.

In 2010, Congress enacted the Biologics Price Competition and Innovation Act (BPCIA), creating an abbreviated approval pathway for biosimilars while maintaining 12 years of data protection to incentivize the development of new innovative biologics. This framework has provided more options for patients, increased access to lifesaving medications, and lowered health care costs through additional competition in the marketplace.

For a biosimilar drug to receive FDA approval, it must be highly similar to the original biological drug and contain no clinically meaningful differences, although there may be minor differences in clinically inactive ingredients. According to the National Cancer Institute, the biosimilar also must prove to be "as safe as, work as well as, and work in the same way as" the original drug, and "be used in the same way, at the same dose, and for the same condition."

Generic drugs are chemically identical to the original branded drug and, as such, cost significantly less because they don't require much testing. Because biosimilars are made from living organisms, though, and don't contain identical ingredients to their name-brand counterparts, they still require some testing. So, they cost more than generics, but less than the branded biologic. Unlike with generic drugs of the more common small-molecule type, biologics generally exhibit high molecular complexity and may be quite sensitive to changes in manufacturing processes. Despite that heterogeneity, all biopharmaceuticals, including biosimilars, must maintain consistent quality and clinical performance throughout their lifecycle. A biosimilar is not regarded as a generic of a biological medicine. This is mostly because the natural variability and more complex manufacturing of biological medicines do not allow an exact replication of the molecular micro-heterogeneity.

In general, generic drugs cost 40 percent to 50 percent less than the brand product. Biosimilars, in contrast, are closer to 15 percent to 20 percent cheaper because of the amount the drug manufacturer has to spend on testing. But because there are potential cost savings to the drug industry as a whole, I think we'll see a slow-moving shift toward using biosimilars more and more in the future.

So far, the FDA has approved 12 biosimilars. The first was filgrastim-sndz (Zarxio™), approved in 2015 as a derivative of the branded drug filgrastim (Neupogen®), which is used to prevent infection during chemotherapy. The drug bevacizumab-awwb (Mvasi™), modeled after bevacizumab (Avastin®), was the first biosimilar approved for cancer treatment, in 2017. The next biosimilar coming down the pike, which will be on the market in 2019, is trastuzumab-dkst (Ogivri™), a biosimilar developed from trastuzumab (Herceptin®).

Drug-related authorities such as the EU's European Medicines Agency (EMA), the US's Food and Drug Administration (FDA), and the Health Products and Food Branch of Health Canada hold their own guidance on requirements for demonstration of the similar nature of two biological products in terms of safety and efficacy. According to them, analytical studies demonstrate that the biological product is highly similar to the reference product, despite minor differences in clinically inactive components, animal studies (including the assessment of toxicity), and a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics). They are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and is intended to be used and for which licensure is sought for the biological product.

The World Health Organization (WHO) published its "Guidelines for the evaluation of similar biotherapeutic products (SBPs)" in 2009. The purpose of this guideline is to provide an international norm for evaluating biosimilars with a high degree of similarity with an already licensed, reference biotherapeutic medicine. The European Union was the first region in the

world to develop a legal, regulatory, and scientific framework for approving biosimilar medicines. The EMA has granted a marketing authorization for more than 50 biosimilars since 2006 (first approved biosimilar Somatropin (Growth hormone)). The first monoclonal antibody that was approved in 2013 was infliximab, putting the EU at the forefront of biologics regulatory science. Meanwhile, on March 6, 2015, the FDA approved the United States's first biosimilar product, the biosimilar of filgrastim called filgrastim-sndz (trade name Zarxio) by Sandoz.

Approval processes

Approval of medicines in the EU relies on a solid legal framework, which in 2004, introduced a dedicated route for the approval of biosimilars. The EU has pioneered the regulation of biosimilars since the approval of the first one (the growth hormone somatropin) in 2006. Since then, the EU has approved the highest number of biosimilars worldwide, and consequently has the most extensive experience of their use and safety. All medicines produced using biotechnology and those for specific indications (e.g. for cancer, neurodegeneration and auto-immune diseases) must be approved in the EU through the EMA (via the so-called 'centralised procedure'). Nearly all biosimilars approved for use in the EU have been approved centrally, as they use biotechnology for their production.

In the United States, the Food and Drug Administration (FDA) held that new legislation was required to enable them to approve biosimilars to those biologics originally approved through the PHS Act pathway. The FDA gained the authority to approve biosimilars (including interchangeables that are substitutable with their reference product) as part of the Patient Protection and Affordable Care Act signed into law by President Obama on March 23, 2010. The FDA has previously approved biologic products using comparability, for example, Omnitrope in May 2006, but this like Enoxaparin was also to a reference product, Genotropin, originally approved as a biologic drug under the FD&C Act.

In March 2020, most protein products that were approved as drug products (including every insulin currently on the market as of December 2019) are scheduled to open up to biosimilar and interchangeable competition in the United States. However, "chemically synthesized polypeptides" are excluded from this transition, which means that a product that falls within this category won't be able to come to market as a biosimilar or interchangeable product, but will have to come to the market under a different pathway.

Background

Cloning of human genetic material and development of in vitro biological production systems has allowed the production of virtually any recombinant DNA based biological substance for eventual development of a drug. Monoclonal antibody technology combined with recombinant DNA technology has paved the way for tailor-made and targeted medicines. Gene- and cell-based therapies are emerging as new approaches.

Recombinant therapeutic proteins are of a complex nature (composed of a long chain of amino acids, modified amino acids, derivatized by sugar moieties, folded by complex mechanisms). These proteins are made in living cells (bacteria, yeast, animal or human cell lines). The ultimate characteristics of a drug containing a recombinant therapeutic protein are to a large part determined by the process through which they are produced: choice of the cell type, development

of the genetically modified cell for production, production process, purification process, formulation of the therapeutic protein into a drug.

After the expiry of the patent of approved recombinant drugs (e.g., insulin, human growth hormone, interferons, erythropoietin, monoclonal antibodies and more) any other biotech company can develop and market these biologics (thus called biosimilars). Every biological (or biopharmaceutical products) displays a certain degree of variability, even between different batches of the same product, which is due to the inherent variability of the biological expression system and the manufacturing process. Any kind of reference product has undergone numerous changes in its manufacturing processes, and such changes in the manufacturing process (ranging from a change in the supplier of cell culture media to new purification methods or new manufacturing sites) was substantiated with appropriate data and was approved by the EMA. In contrast, it is mandatory for biosimilars to take a both non-clinical and clinical test that the most sensitive clinical models are asked to show to enable detection of differences between the two products in terms of human pharmacokinetics (PK) and pharmacodynamics (PD), efficacy, safety, and immunogenicity.

The current concept of development of biosimilar mAbs follows the principle that an extensive state of the art physicochemical, analytical and functional comparison of the molecules is complemented by comparative non-clinical and clinical data that establish equivalent efficacy and safety in a clinical "model" indication that is most sensitive to detect any minor differences (if these exist) between biosimilar and its reference mAb also at the clinical level.

The European Medicines Agency (EMA) has recognized this fact, which has resulted in the establishment of the term "biosimilar" in recognition that, whilst biosimilar products are similar to the original product, they are not exactly the same. Every biological displays a certain degree of variability. However, provided that structure and function(s), pharmacokinetic profiles and pharmacodynamic effect(s) and/or efficacy can be shown to be comparable for the biosimilar and the reference product, those adverse drug reactions which are related to exaggerated pharmacological effects can also be expected at similar frequencies.

Originally the complexity of biological molecules led to requests for substantial efficacy and safety data for a biosimilar approval. This has been progressively replaced with a greater dependence on assays, from quality through to clinical, that show assay sensitivity sufficient to detect any significant difference in dose. However, the safe application of biologics depends on an informed and appropriate use by healthcare professionals and patients. Introduction of biosimilars also requires a specifically designed pharmacovigilance plan. It is difficult and costly to recreate biologics because the complex proteins are derived from living organisms that are genetically modified. In contrast, small molecule drugs made up of a chemically based compound can be easily replicated and are considerably less expensive to reproduce. In order to be released to the public, biosimilars must be shown to be as close to identical to the parent innovator biologic product based on data compiled through clinical, animal, analytical studies and conformational status.

Generally, once a drug is released in the market by the FDA, it has to be re-evaluated for its safety and efficacy once every six months for the first and second years. Afterward, re-evaluations are conducted yearly, and the result of the assessment should be reported to authorities such as FDA. Biosimilars are required to undergo pharmacovigilance (PVG) regulations as its reference product. Thus biosimilars approved by the EMA (European

Medicines Agency) are required to submit a risk management plan (RMP) along with the marketing application and have to provide regular safety update reports after the product is in the market. The RMP includes the safety profile of the drug and proposes the prospective pharmacovigilance studies.

Several PK studies, such as studies conducted by Committee for Medicinal Products for Human Use (CHMP), have been conducted under various ranges of conditions; Antibodies from an originator's product versus antibodies from an biosimilar; combination therapy and monotherapy; various diseases, etc. on the purpose to verify comparability in pharmacokinetics of the biosimilar with the reference medicinal product in a sufficiently sensitive and homogeneous population. Importantly, provided that structure and function(s), pharmacokinetic profiles and pharmacodynamic effect(s) and/or efficacy can be shown to be comparable for the biosimilar and the reference product, those adverse drug reactions which are related to exaggerated pharmacological effects can also be expected at similar frequencies.

FDA's Role in Ensuring Access to Safe and Effective Options for Patients

To date, the FDA has issued numerous draft and final guidance documents to provide clarity to biosimilar manufacturers regarding the data needed to support applications to FDA for biosimilar and interchangeable biologic products. The FDA approved the first biosimilar product for marketing in the United States in March 2015. Recognizing biosimilars' important role, in 2018 the FDA introduced the Biosimilars Action Plan to help spur additional competition.

This plan focuses on four areas of FDA activities:

1) Improving the efficiency of the biosimilar and interchangeable product development and approval process;

2) Maximizing scientific and regulatory clarity for the biosimilar product development community;

3) Developing effective communication to improve understanding of biosimilars among patients, clinicians, and payors; and

4) Supporting market competition.

Increasing Competition For Biologics and Biosimilars

The U.S. biologics and biosimilars market is evolving rapidly, and the benefits for patient access and controlling health care costs will continue to grow over time as more medicines are introduced. As of February 2020, there are 14 biosimilars on the market in the U.S. competing against 7 reference biologics, with 13 additional FDA approved biosimilars due to come to market over the next several years. As of December 2019, there were 74 programs enrolled in the in the Biosimilar Product Development (BPD) Program. The rich pipeline of potential biosimilar and interchangeable products currently in development as well as current market experience indicates that there is still significant potential for cost savings in the United States market.

Recent studies project that biosimilars could significantly reduce spending in the U.S. health care system. Mulcahy et al. have projected that the use of biosimilars will reduce spending on biologic drugs by $54 billion from 2017 to 2026, and the IQVIA Institute estimates the U.S. health care system will save $160 billion due to biosimilar competition over the next 5 years.

Biosimilars are already realizing their promise, leading to lower prices and savings for patients. A recent analysis of the market dynamics of four biologics and their biosimilars demonstrated that the net prices of all the originator biologics decreased following the entry of biosimilars.

As the market experience with biosimilars increases, we expect product usage to play in expanded role in options for patients and further decrease prescription drug spending. Experts have argued that the coming wave of biosimilars will penetrate the market even more quickly than those already available for patients.