The Basic of Biosimilars

Introduction

Biologics—drugs created from living organisms—are considered by many to be the future of pharmaceutical medicine because of their innovative nature and effectiveness.[1] These treatments, however, come with a significant price tag. Despite only being used by two percent of the population, brand-name biologics account for nearly 40 percent of all U.S. pharmaceutical sales and are a major driver of the unsustainable growth in domestic prescription drug spending.[2]

Biosimilars, commonly understood as near copies of brand-name biologics, have the potential to bring down those costs through competition. But so far, the U.S. has failed to foster a robust market for biosimilars. The following brief provides a general overview of biosimilars and how they are approved and regulated domestically before turning to an examination of the U.S. market for biosimilars and current barriers keeping this market from flourishing. It concludes by underscoring the issues policymakers must address to improve access to biosimilars.

THE BASICS OF BIOSIMILARS

Biologics are medicines that are created with natural materials—such as cells—from humans, animals, or other living organisms.[3] One important way these medicines differ from small molecule drugs, which are made from chemicals, is that biologics are not easily copied due to their complex nature.[4] While a small molecule medicine can be recreated exactly—and is referred to as a "generic" when that medicine is copied from a brand-name drug—a biologic cannot be replicated in such an exact way.

A biosimilar then is not identical to a biologic, which is often referred to as the "reference" product for the biosimilar. Instead, biosimilars are highly similar and have "no clinically meaningful differences" to the reference biologic.[5] Being deemed a biosimilar, however, does not automatically mean that the biosimilar is "interchangeable," meaning that the product can be substituted for the reference biologic by a pharmacist without a patients' health provider being involved, with the biologic.[6] The implications of this distinction will be discussed more below.

Licensing of Biosimilars

As with traditional drugs, the Food and Drug Administration (FDA) regulates the approval (known as licensing in this context) process for both biologics and biosimilars.[7] Generally, to be marketed in the U.S., any biological product must submit a Biologics License Application (BLA). This application must contain a variety of information on the treatment itself as well as where and how it will be manufactured. A successful application must prove to the FDA that the biologic is "safe, pure, and potent."[8]

In 2010, as part of the Affordable Care Act (ACA), Congress created a streamlined process for the licensure of biosimilars known as the Biologics Price Competition and Innovation Act (BPCIA).[9] Instead of having to go through the full BLA process that new brand-name biologics are required to submit, BPCIA authorizes manufacturers of biosimilars to submit abbreviated application information demonstrating that, even if there are small differences in the makeup of the product, the biosimilar is highly similar to the reference biologic.[10] The FDA has significant discretion in determining what tests and studies are necessary to show this similarity and establish the biosimilar's own safety, purity, and potency.[11]

For products seeking to be considered interchangeable with the reference biologic, the manufacturer must also demonstrate that the product "can be expected to produce the same clinical result as the reference product in any given patient."[12] In May of 2019, the FDA finalized long-awaited guidance for industry on how to meet this standard.[13] The guidance included information on factors the FDA would consider in determining interchangeability as well as the type and volume of studies that would generally be needed for the consideration process.[14]

THE U.S. MARKET FOR BIOSIMILARS

To date, 23 biosimilars have been licensed by the FDA,[15] though less than half of these products are actually on the market.[16] The FDA has not yet approved any biosimilars as interchangeable.[17]

The U.S. market for biosimilars lags our European counterparts significantly, where there are more than double the number of biosimilars on the market.[18] And even when biosimilars are licensed by the FDA, many face anti-competitive challenges that prevent these products from actually entering the U.S. market as well as additional barriers even if on the market that may disincentivize their use.[19]

Barriers to Bringing Biosimilars to Market

Brand-name manufacturers engage in several anti-competitive behaviors designed to keep biosimilars off the market, using both exclusivity and patent protections to their benefit. Exclusivity refers to the number of years set by the FDA that a new biologic enjoys once approved (12 for biologics).[20] Patents, however, are overseen by the U.S. Patent and Trademark Office, run for 20 years from patent application, and can be obtained at any point in the lifecycle of a drug.[21] Both exclusivity and patent protections are used to block competition during the years in effect.

These behaviors are perhaps most clearly illustrated by the drug manufacturer AbbVie's actions in regard to the biologic Humira—the original exclusivity and patent periods of which have ended.[22] Humira, developed to treat rheumatoid arthritis, is both one of the most expensive drugs on the market as well as being widely used, making AbbVie's tactics all the more notable.[23]

For example, "patent thicketing" is when manufacturers apply for a variety of possibly superficial patents near the end of a patent period to extend their monopoly over a treatment. AbbVie, without any significant change to Humira, has applied for 247 new patents and has been granted 132.[24] In addition, it has been reported as engaging in "pay-for-delay" tactics, which is when a brand-name drug enters into an agreement with a potential competitor not to come to market. In AbbVie's case, it has entered into such agreements with at least eight potential biosimilar manufacturers that are in effect until 2023. These agreements are subject to some government oversight but are still largely opaque.[25]

BPCIA contained protections for biosimilar manufacturers against some of these tactics in regard to biologic products approved after 2010.[26] But currently, all approved biosimilars reference biologics were on the market before 2010. As a result, many questions remain in regard to what impact these specific BPCIA protections will have on the biosimilars market.

Barriers to Biosimilar Uptake in Medicine[27]

Increasing the utilization of biosimilars, and eventually of interchangeables, is essential in order to reduce drug spending. But while patients and their providers need to be confident that they can use these products safely in the place of the reference biologics, current policies and market realities may stand in the way of this.

Under the BPCIA, biosimilars are only meant to be substituted for a reference biologic at the discretion of a prescriber, while interchangeable products are theoretically substitutable at the pharmacy. But the total lack of interchangeables on the market prevents pharmacists from being able to substitute a lower-cost biosimilar in the place of biologic without an explicit prescription.[28] Not only does this potentially hinder substitution, but it also can contribute to both provider and patient confusion at the point of prescription if a biosimilar is as safe and effective as the biologic.[29] It has yet to be seen if the newly released guidance from the FDA on interchangeability will lead to the submission of applications for interchangeable products and ultimately to their approval by the FDA.

In addition, it is important to note that even as interchangeable products are approved, several states have passed proactive "anti-substitution laws" that will make it difficult for interchangeable products to be easily dispensed in the place of a more expensive biologic.[30]

Further, the FDA's naming and labeling requirements can operate to differentiate a biosimilar from its reference biologic, which the FDA says is necessary to ensure proper use of and surveillance of these products but may undermine the confidence of providers and patients that the FDA believes these products will work as well as their reference biologics. Currently, biologics and biosimilars have different labeling requirements, which may send conflicting signals about the appropriateness of choosing a biosimilar over a biologic.[31] While there is continuing debate in regard to what labeling information is appropriate, the FDA has been most recently engaged in issuing guidance in regard to the naming of biologics, biosimilars, and interchangeable products.

In March of 2019, the FDA issued draft guidance on naming. Newly licensed reference biologics, biosimilars, and interchangeables will share a "core name" with suffixes of four letters added onto the end of that name indicating each product's status as a biologic, biosimilar, or interchangeable product.[32] Biologic products previously approved, however, will not be subject to this requirement.[33] While the use of a core name has been generally welcomed by those that support access to biosimilars, the use of different suffixes raises concerns that providers and patients will continue to be confused on if biologics and biosimilars can be substituted for one another.[34]

CONCLUSION: MUCH WORK TO BE DONE

Policymakers have made efforts to improve access to biosimilars. But while bipartisan legislation on biosimilars continues to be introduced in Congress and the now-departed Commissioner Gottlieb has published an FDA "Biosimilar Action Plan,"[35] these actions have not yet brought a significant expansion in access to biosimilars.

Both legislative and regulatory policymakers must take action to prohibit anti-competitive behaviors such as patent thicketing and opaque settlement agreements between biologic and biosimilar manufacturers, ease confusion on the appropriateness of prescribing a biosimilar, and ensure that once interchangeable products are approved they can be substituted without undue difficultly.

With the importance biologics hold for patients' health and financial well-being as well as for health care system costs as a whole, it is a priority to ensure biosimilars are properly brought into U.S. markets to spur competition and lower spending across the board.

ENDNOTES

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7 While not the focus of this brief, it is worth noting that biologics—which, despite being thought of as being at the forefront of pharmaceutical innovation, have actually been in existence for decades—have a complex and interesting regulatory history that began at the National Institutes of Health (NIH) before oversight of these products was transferred to the FDA in 1972. Congressional Research Service, "Biologics and Biosimilars: Background and Key Issues," June 2019, https://fas.org/sgp/crs/misc/R44620.pdf.

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