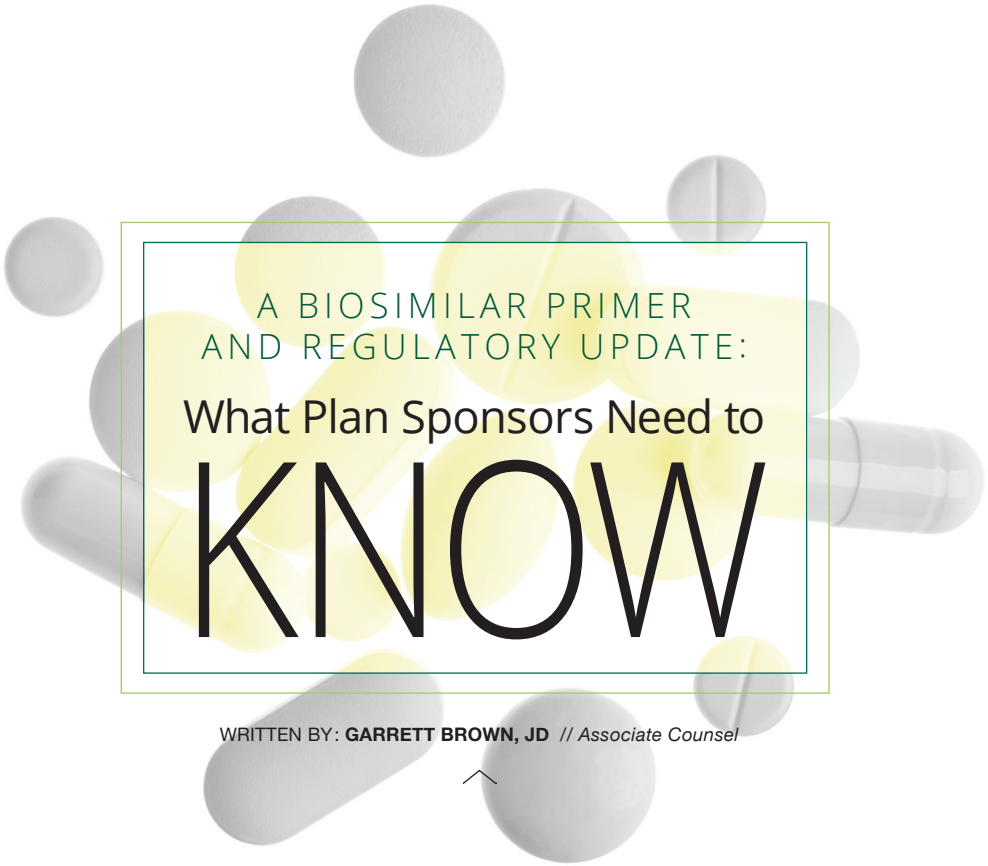

A BIOSIMILAR PRIMER AND REGULATORY UPDATE: What Plan Sponsors Need to KNOW

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In late June 2017, the Supreme Court issued a 9-0 opinion in *Sandoz v. Amgen,* an opinion that can be seen as a win for biosimilar drug manufacturers. This decision presents an excellent opportunity to provide a refresher on what a biosimilar drug is and why plans need to keep abreast of any developments in this industry.

A rudimentary way to describe a biosimilar is that it is a generic specialty drug. An understanding of how generic and biosimilar medications come to market is important. While similarities exist, the unique nature of biologics and the relatively recent regulatory scheme for their entry into the market resulted in *Sandoz v. Amgen*. This article will provide a summary of what a biosimilar drug is, a biosimilar drug's path to market, an overview of *Sandoz v. Amgen* and how plans should respond.

What is a biosimilar?

Biological products include a wide range of products, such as vaccines, blood components, allergenics, gene therapy and recombinant therapeutic proteins. In contrast to small-molecule non-biologic drugs that are chemically synthesized and their structure is known, most biologics are large-molecule drugs created by complex mixtures and processes that are not easily identified or characterized. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. The development of a large molecule drug is a risky and costly process for a manufacturer. Figures vary, but the cost to develop these products may exceed a billion dollars and may take more than 10 years to complete.

PLAN SPONSORS HAVE BEEN IMPACTED BY SOME OF THESE HIGH-COST PRODUCTS AS PART OF THEIR SPECIALTY SPEND.

While a concrete definition of a specialty drug is a moving target, most biologics are deemed specialty drugs, but not all specialty drugs are biologics.

A biosimilar product is a biological product that is approved based on showing that it is highly similar to a Food and Drug Administration (FDA)-approved biological product, known as a reference product. It has no clinically meaningful differences in terms of safety and efficacy from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products. An interchangeable biological product is biosimilar to an FDA-approved reference product and meets additional standards for interchangeability. An interchangeable biological product may be substituted for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product.

A biosimilar's path to market

For small-molecule drugs, the Hatch Waxman Act (HWA) of 1984 governs the FDA approval process for generic medications and creates a pathway that allows generic drugs to be approved based on their bioequivalence. The HWA expedited process allows a generic manufacturer to forgo clinical trials to demonstrate safety and efficacy of its bioequivalent products. As discussed below, the biosimilar approval process may appear similar to the approval process for a generic small-molecule drug, but while a biosimilar drug needs only to be highly similar, a generic small-molecule drug must demonstrate that its active ingredients, strength and dosage from are identical.

In the face of significant growth in the biologic space and an understanding that a biosimilar medication is not identical to its reference product, Congress enacted the Biologics Price Competition and Innovation Act (BPCIA) as part of the Affordable Care Act (ACA). The BPCIA creates a regulatory framework designed to create an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product. While the FDA-licensed reference product is provided with market exclusivity for 12 years and an additional six months if the product is approved for pediatric use, the BPCIA's abbreviated process allows the applicant to piggyback on the showing made by the manufacturer of a previously licensed biologic.

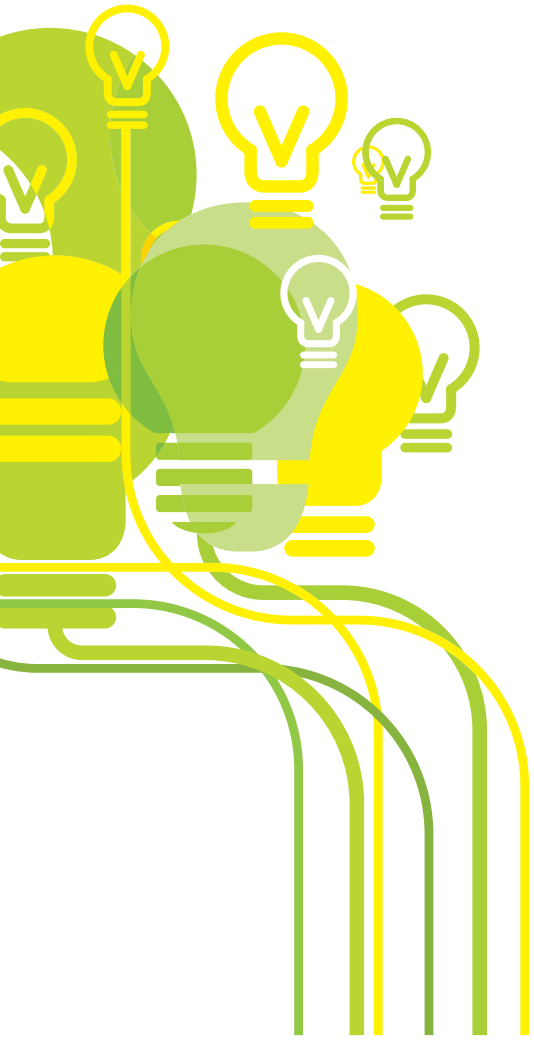
As the reference product nears the end of this exclusivity period, manufacturers seeking to introduce a biosimilar product begin an application process under the BPCIA's abbreviated pathway. The applicant must provide notice to the reference product manufacturer within 20 days of the date the applicant is notified by the FDA that its application has been accepted for review. Following this notice, the applicant and reference product manufacturer exchange information so that the reference product manufacturer can identify if any intellectual property has been inappropriately copied by the applicant. Despite the lapse of the exclusivity period, the reference product manufacturer may hold multiple patents covering the biologic, including the processes used to manufacture it. These patents may constrain an applicant's ability to market its biosimilar even after the expiration of the exclusivity period. This nuance represents the need for an alternative pathway.

In anticipation of the need to address these intellectual property issues, the BPCIA then channels the parties into two phases of patent litigation. In the first phase, the parties collaborate to identify patents for immediate litigation. Upon the applicant's notice to begin marketing the biosimilar commercially, the second phase is initiated and involves any patents not litigated in the first phase. The applicant's notice of commercial marketing is required to be provided to the reference drug manufacturer not later than 180 days before the date of the first commercial marketing of the biological product. Failure to comply with the regulatory construct allows the reference drug manufacturer to bring immediate litigation for declaratory action and litigate any patent infringement issues that would otherwise be off the table under the BPCIA construct.

Sandoz v. Amgen

A reference drug manufacturer reading the BPCIA, prior to *Sandoz v. Amgen,* may assume that it would have an additional six-month window from the time a biosimilar product is licensed until the biosimilar product is commercially marketed. This timing was challenged in *Sandoz v. Amgen* and ultimately argued before the Supreme Court earlier this year. In this court case, Sandoz, a generic pharmaceutical company, sought a license from the FDA to market Zarxio, which is a drug used to help the body make white blood cells after receiving cancer medications. Zarxio is a biosimilar of Amgen's drug, Neupogen. However, Amgen contested what it believed to be Sandoz's failure to comply with the BPCIA process because Sandoz (1) did not provide application and manufacturing information to the reference manufacturer and (2) provided its notice to market concurrently with the application and prior to obtaining a license from the FDA to manufacture its biosimilar product. Regarding the first issue the court held only that a federal court could not grant an injunction to Amgen, the reference product manufacturer, that would require Sandoz's information be turned over to Amgen. It deemed this disclosure to not be mandatory following application if the applicant did not wish to utilize the BPCIA process. In the second issue, the court held that an applicant may provide notice before obtaining approval.

Certainly, one can see the desire of Sandoz to not share its application and manufacturing information with the reference manufacturer, especially if its product and manufacturing processes may be the subject of litigation outside of the BPCIA's framework. Moreover, one can recognize its desire to commercially market its product as soon as possible. Conversely, one can appreciate when a reference product manufacturer seeks to vigorously protect its intellectual property and delay the entry of a competitor into the market. In the face of a pipeline full of biosimilar drugs, these dynamics will likely give rise to more legislation in the future.



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What does all of this mean for plan sponsors?

This ruling signals that some biosimilar drugs may be coming to market prior to what some may otherwise have anticipated, especially in situations where there is no patent infringement and the FDA approval process takes more than 180 days. As with the small-molecule generic drugs, savings from a single biosimilar entrant may be initially limited, but this entry is only the beginning of downward cost pressure as additional entrants enter the market. In the face of accelerating specialty drugs, any downward cost pressure will be welcome relief for plan sponsors.

From a medical management perspective, it is important to understand if a plan sponsor's medical plan administrator is engaging with physicians to educate and ensure that any value from biosimilar drugs can be realized by the plan and its participants. As physician payment arrangements are generally based on a percentage of average sales price, physicians are faced with little incentive to evaluate and administer biosimilar medications over their reference product counterparts. For example, in 2016, the FDA approved biosimilar, Inflectra, which is approximately 10 to 15 percent cheaper than its reference product, Remicade. It is important to understand how the medical vendor is addressing the entry of biosimilar drugs and promoting the use thereof.

From a prescription benefit management perspective, this ruling is another example of the complexity that exists in the prescription drug marketplace. The complex supply chain that supports this market must carry on and proceed in the face of such uncertainty. This compounds the need to understand the bigger picture and how the prescription drug market operates. While this complexity is nothing new, it emphasizes the need to approach this market in a very different manner than other health and welfare benefits. The ability to quickly respond to these market changes will be important to capture the value that biosimilars offer. This response must take the form of plan sponsors ensuring that their plan designs and contracts are able to respond to such entries. From a plan design perspective, this necessitates the need to have an actionable plan to incentivize the use of these medications. From a contracting perspective, this reinforces the value of a market check provision that allows a prescription drug services contract to be renegotiated and adjusted based on market conditions. Ultimately, having the correct partner is the key to managing this complex and shifting landscape.

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