Portfolio Media. Inc. | 111 West 19th Street, 5th Floor | New York, NY 10011 | www.law360.com
Phone: +1 646 783 7100 | Fax: +1 646 783 7161 | customerservice@law360.com

FDA Biosimilars Plan Draws From Experience With Generics

By **Maria Doukas, Christopher Betti, Kathleen Sanzo, Jacqueline Berman and Michael Abernathy** (August 20, 2018, 2:29 PM EDT)

Maria Doukas

Christopher Betti

Kathleen Sanzo

Jacqueline Berman

On May 11, 2018, President Donald Trump issued his blueprint to lower drug prices that describes the Administration's plan to reduce the price of prescription drugs by, among other actions, "[a]dvanc[ing] biosimilars and generics to boost price competition."[1] The blueprint "seek[s] to encourage innovation, while also promoting better price competition."[2] To help achieve the administration's goals, the U.S. Food and Drug Administration recently unveiled the FDA's Biosimilars Action Plan, which FDA Commissioner Scott Gottlieb called "an important piece" of the blueprint.[3][4] Noting the "anemic" competition for biosimilars with only three biosimilars currently marketed in the U.S. 11 being FDA approved at the time of the BAP release,[5] Commissioner Gottlieb stated the BAP would help the FDA achieve the goals of "mak[ing] the process for developing biosimilars more efficient" and "promoting competition and affordability across the market for biologics and biosimilar products."[6]

According to the FDA, over the years, biologics have increasingly been established as a mainstay of medical treatment for many serious diseases and conditions.[7] At this same time, as stated by Commissioner Gottlieb, biologic treatment can be expensive.[8] Moreover, according to Commissioner Gottlieb, biologics represented 70 percent of the growth in drug spending from 2010 to 2015 and they are forecast to be the fastest growing segment of drug spending in future years.[9]

Recognizing the importance of biologics, Congress passed the Biologics Price Competition and Innovation Act of 2009, creating an abbreviated pathway for the approval of biosimilar products, which are biologics that, notwithstanding minor differences in clinically inactive components, are highly similar to and have no clinically meaningful differences from an existing FDA-approved biological product.[10] In the nine years since the passage of the act, however, the number of biosimilars approved has been small.

Thus, the BAP provides the FDA's framework to "accelerate biosimilar competition with four key strategies": (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 communications to improve understanding of biosimilars among patients, providers and payors; and (4) supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay market competition to follow-on products.[11]

To achieve these four key strategies, the BAP outlines different priority deliverables. For example, to achieve the first strategy of improving the efficiency of the biosimilar and interchangeable product development and approval process, the FDA is internally reorganizing and is developing application review templates specific for Section 351(k) biosimilar license applications to help streamline the FDA review process."[12] Further, the FDA states that it will also develop information resources and development tools to assist with biosimilar and interchangeable product development, including an index of biosimilar critical quality attributes to allow sponsors to better understand how the FDA evaluates data from comparative analytical studies.[13] The FDA also aims to develop and validate pharmacodynamic biomarkers and computer modeling and simulation to evaluate pharmacokinetic and pharmacodynamic response versus clinical response using existing clinical data.[14] Ultimately, the FDA states that these steps "can allow development programs to be more efficient and can reduce the size of clinical studies" of biosimilar products.

Notably, shortly before the release of the BAP, the FDA withdrew its draft guidance for industry entitled "Statistical Approaches to Evaluate Analytical Similarity"[15] based on industry comments that the guidance could impact the cost and efficiency of biosimilar development, including the number of reference product lots that should be sampled as part of an evaluation of high similarity and statistical methods for this evaluation.[16]

Additionally, to achieve the second strategy of maximizing scientific and regulatory clarity, the FDA plans to enhance the Purple Book to include more information about approved biological products, develop additional guidance documents, engage in rulemaking and hold public meetings and hearings to seek additional input to further clarify the regulatory pathway for biosimilar and interchangeable products.[17] Guidance documents will include those providing clarity to biosimilar manufacturers on how to "carve out" conditions of use from their labels that may be covered by an active patent to help facilitate earlier biosimilar market entry.[18] The FDA also intends to use real-world evidence as support for safety assessments and prescribing of biosimilars, which would be gathered from existing FDA databases, and through partnerships with private and public insurers.[19] Finally, and significantly, under the second strategy, the FDA intends to strengthen partnerships with foreign regulatory agencies, potentially through data sharing agreements to obtain data on biosimilar real world use and to increase the use of non-U.S.-licensed comparator products in studies to support biosimilar marketing applications.[20] The impact of data-sharing with the EU is significant as substantially more biosimilar products are authorized in the European Union[21] and could open the door for biosimilar sponsors to leverage existing data and studies from these other markets.

To achieve the third strategy of developing effective communications to improve the understanding of biosimilars, the FDA plans to proactively educate clinicians, patients and payors, including by releasing educational materials and a webinar, as well as utilizing social media.[22] Finally, to achieve the fourth strategy of supporting market competition, the FDA plans to coordinate with the Federal Trade Commission to address "anti-competitive behavior," as well as work with legislators to close loopholes that may delay biosimilar competition.[23] FDA further will address circumstances in which manufacturers refuse to sell samples, or use other strategies, to delay biosimilar market entry and competition.[24]

Although the BAP provides strategies and proposed deliverables that Commissioner Gottlieb claimed is "aimed at promoting competition and affordability across the market," it does not address issues that the FDA admits negatively impact this competition, including (1) "rebating schemes" and (2) "patent thickets" resulting in litigation-delayed market entry.[25] Indeed, these issues fall outside the FDA's

jurisdiction, resulting in the BAP merely providing (1) regulatory strategies that the FDA may implement to help improve clarity and streamline the application process for biosimilars and (2) a proposal to coordinate with the FTC or legislators without providing concrete plans to effectively coordinate or leverage a combined effort to foster biosimilar competition.

Moreover, Commissioner Gottlieb acknowledged that with regard to improving the market pathway for biosimilars, "FDA can't do it alone" and "[e]ffective market competition from biosimilars depends on additional actions from our public and private sector partners to align reimbursement and formulary design to encourage appropriate biosimilar adoption."[26] Thus, the impact that the BAP will have in alleviating the "anemic" competition in the biosimilars space is unclear.

Interestingly, in mid-2017, the FDA released a Drug Competition Action Plan, or DCAP, focused on generic drugs. At its core, the DCAP shares the same goals as the BAP: advance policies promoting robust generic entry to lower drug prices. Thus, not surprisingly, the FDA applied similar strategies in the DCAP and the BAP.[27] Indeed, in both the DCAP and the BAP, the FDA recognized that a lack of regulatory clarity can inhibit market entry and that regulatory rules can be gamed to stifle and limit generic competition, so both discuss working with the FTC to prevent anti-competitive behavior. Moreover, the DCAP and the BAP both discuss streamlining regulatory review procedures.[28]

In the short time since the FDA released the DCAP, FDA statistics show that between fiscal year 2017 and 2018 there is a 23 percent decrease in the number of abbreviated new drug applications received; a 67 percent increase in the number of complete response letters; and no significant increase in ANDA approvals (including tentative approvals).

FDA Fiscal Year	ANDAs Received	CRLs	Approvals and Tentative Approvals
FY 2015[29]	539	1,180	612
FY 2016[30]	852	1,725	835
FY 2017[31]	1,306	1,603	937
FY 2018[32]	1,009*	2,669*	936*

* Annualized for remainder of FDA fiscal year

Thus, although still very much in its infancy, it remains to be seen what impact the DCAP will have on increasing ANDA approvals.

However, the impact of the DCAP on generics will likely not foreshadow what is to come in the biosimilars field following the BAP's release due to key differences between generics and biosimilars that may result in the BAP faring better at achieving its stated objectives. For instance, differences in the quality and robustness of biosimilar applications versus ANDAs and the much smaller number of filed biosimilar applications (6 filed biosimilar applications versus 1,306 filed ANDAs in 2017) may assist the FDA in shortening regulatory review and increasing approvals. Consequently, time will tell if the BAP is able to achieve its goal of promoting biosimilar products.

Maria E. Doukas is an associate at Morgan Lewis & Bockius LLP.

Christopher J. Betti is a partner at the firm.

Kathleen M. Sanzo is a partner at the firm.

Jacqueline R. Berman is an associate at the firm.

Michael J. Abernathy is a partner at the firm.

[1] President Donald J. Trump's Blueprint to Lower Drug Prices, May 11, 2018, available at https://www.whitehouse.gov/briefings-statements/president-donald-j-trumps-blueprint-lower-drug-prices/.

[2] Id.

[3] "Dynamic Regulation: Key to Maintaining Balance Between Biosimilars Innovation and Competition," Remarks by Scott Gottlieb, M.D., Commissioner of Food and Drugs, July 18, 2018, available at https://www.fda.gov/NewsEvents/Speeches/ucm613452.htm.

[4] FDA also has a public hearing on "FDA's approach to facilitating greater availability of biosimilar and interchangeable products" scheduled for September 4, 2018.
See https://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/default.htm.

[5] As of the date of this article, there are now 12 biosimilars approved by FDA.

[6] See supra note 3.

[7] Id.

[8] Id.

[9] Id.

[10] 42 U.S.C. § 262(i)(2).

[11] See supra note 3.

[12] Biosimilars Action Plan: Balancing Action & Competition, July 2018, at 5, available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm613761.pdf.

[13] Id. at 6.

[14] Id.

[15] FDA Withdraws Draft Guidance for Industry: Statistical Approaches to Evaluate Analytical Similarity, June 21, 2018, available at https://www.fda.gov/Drugs/DrugSafety/ucm611398.htm.

[16] Id.

[17] See supra note 11 at 6-7.

[18] Id. at 7.

[19] Id.

[20] Id.

[21] The European Medicines Agency first authorized a biosimilar via the centralized procedures in 2006. European Medicines Agency, European Public Assessment Reports, available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125(last accessed Aug. 3, 2018). As of August 3, 2018, 44 biosimilars had been approved using the centralized procedures.

[22] See supra note 11 at 8.

[23] Id.

[24] Id. at 9.

[25] See supra note 3.

[26] Id.

[27] Id.

[28] Id.