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What Current Legal Developments Mean For Biosimilars

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Law360, New York (April 20, 2017, 4:30 PM EDT) -- In an ever fast paced and changing world, legal thinkers and practitioners must not only keep up with the changing laws and legal dynamics but stay ahead of them. This was the theme of the life sciences symposium co-sponsored by Mayer Brown and Seton Hall Law. The symposium, which was the second of its kind, was on March 2, 2017, in Newark, New Jersey. There were panel discussions covering many emerging topics, including the future of biosimilars. You can read another article from the symposium here.

Introduction

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Congress passed the Biologics Price Competition and Innovation Act in 2010, finally paving the way for a long-awaited abbreviated approval pathway in the US for follow-on biologics known as biosimilars. Under the BPCIA, a product is biosimilar if it is highly similar to the reference biological product and there are no clinically meaningful differences between the products. Further, a biosimilar may be interchangeable if the risks are not increased by switching the two products. Under state law, an interchangeable biosimilar may be substituted for the reference biologic, just as generic drugs are currently substituted for branded drugs. The BPCIA also established a specialized procedure for patent litigation addressing alleged infringement by biosimilars, similar in concept to Hatch-Waxman litigation for patents that may be infringed by generic drugs, dubbed "The Patent Dance" for its complex exchange of information relating to the products and patents at issue to the parties.

Seven years have passed since the passage of the BPCIA, yet much of the metes and bounds of the law remains to be determined. To date, only a handful of biosimilar products have been approved, and some of them have not been launched because of ongoing litigation. Until resolved, that litigation will leave significant provisions of the BPCIA to judicial interpretation. In the meantime, while new legislation has passed that is designed to increase the U.S. Food and Drug Administration's resources and speed drug approvals, the new administration has pledged to expedite approvals but reduce the resources of the FDA. In the same vein, on the eve of the new administration the FDA issued one of the most significant BPCIA guidances to date. But the practical effect of this guidance is unclear, as the FDA has considerable latitude in enforcing policy, and FDA guidance by its terms is not binding but merely "reflects the

agency's current thinking" on a topic. Since the agency operates under the direction of the executive, the policy changes proposed by the new administration could have a significant impact on the actual effect of the new guidance.

Those who have watched the development of the BPCIA since the time of its predecessor bills in earlier sessions of Congress have come to accept significant ongoing uncertainty with respect to many facets of the BPCIA. When compared with the development of the Hatch-Waxman generic drug approval pathway decades earlier, this type of evolution is not entirely unexpected. However, we may be approaching a pivotal time for the BPCIA, as a number of critical issues concerning the biosimilars pathway may be resolved relatively soon.

Regulatory Developments: Interchangeability Guidance

Three days before the inauguration of the new administration, the FDA issued a draft guidance addressing the standards for demonstrating interchangeability of biological products under the BPCIA. The FDA had previously issued a number of guidances addressing the standards for establishing biosimilarity, but industry had long been seeking and awaiting instructions addressing the higher standard for interchangeability.

The draft interchangeability guidance provides a detailed set of principles for sponsors seeking to establish a biosimilar as interchangeable. It addressed a number of topics of major concern to potential sponsors of interchangeable biosimilars, including extrapolation of data and the need for switching studies. The guidance calls for an examination of the totality of the circumstances and analysis of residual risks, and also emphasizes that sponsors should consult with FDA frequently throughout the process. This initial interchangeability guidance will likely be followed by additional guidances to clarify and expand on these principles.

The new guidance is a significant step forward in the FDA's progress toward full implementation of the BPCIA. However, interchangeability remains a subject of first impression for all stakeholders. We are a long way away from a biosimilar being found interchangeable. The most significant barrier to a finding of interchangeability is technical, as many scientists and stakeholders believe that technology has not yet developed to the point where such complex molecules can be assessed sufficiently for a determination of interchangeability. With any biologic, there are concerns from a manufacturing standpoint as to how manufacturers can control variability across different cell lines and media. These concerns are magnified with biologics made by different companies, since variability must be controlled across additional factors including different manufacturing facilities.

The possibility of interchangeable biologics has captured the attention of the public. Political leaders have touted biosimilars as another means for significantly lowering drug costs. Thus far in the EU, biosimilars have demonstrated relatively modest price reductions in comparison to those from generic small-molecule drugs. Scores of state legislatures have passed various forms of legislation allowing for the substitution of interchangeable biosimilars under a variety of conditions. The passage of these laws has made headlines, lauded as efforts by political leaders to speed up drug approvals and lower drug costs. But by definition these laws are only applicable to interchangeable products, not biosimilars. Thus, while the eventual licensure of interchangeable biologics implicates many of the same hopes and trepidations as the first generics did in the small molecule industry, it appears that the benefits of such licensing may not be realized until far in the future. How far into the future depends on how the FDA proceeds to craft and implement its interchangeability approval standards, after taking its first step with the issuance of the new draft guidance.

Since the finalization of the draft guidance through the comment process as well as the actual application of the guidance are largely in the discretion of an agency of the executive branch, much of its practical effect will depend on the policy of the new administration.

Legislative Developments: 21st Century Cures

One month before the inauguration of the new administration, Congress enacted the 21st Century Cures Act. The new law included major provisions designed to reduce opioid abuse and support research and drug development, including $4.8 billion in funding to the National Institutes of Health for precision medicine and biomedical research. It also included the Helping Families In Mental Health Crisis Act, considered the most significant attempt at mental health reform in decades. The Cures Act also included provisions concerning Medicare and tax laws applicable to employer health plans.

With respect to the FDA, the Cures Act earmarked $500 million in new funding for the agency, and included provisions intended to expedite the process by such measures as allowing sponsors to rely on data summaries and so-called "real world evidence," which might include observational studies, insurance information and anecdotal data, rather than requiring traditional controlled, blinded clinical trials. Much of the funding is subject to the conventional annual budgeting process. And the relaxed standards, while offering the potential to speed drug and device approvals, have been met with skepticism and criticism by some who believe they amount to a dangerous lowering of standards and thus a risk to patient safety.

Given the role of the executive branch in the budget process and the broad discretion exercised by the FDA as an arm of the executive branch, much of the practical effect of the Cures Act on the future operation of the FDA, and thus the approval pathway for biosimilars, will turn on the policy and actions of the new administration.

Executive Developments: New Administration Policy

The White House has pushed for general deregulation of a variety of agencies, including the FDA. The president specifically called on the FDA in his address to Congress to "slash restraints at the FDA" in order to expedite the marketing of new drug products. The president's selection for FDA commissioner, Dr. Scott Gottlieb, brings a wealth of diverse experience to his new post. He is an internal medicine physician, a former FDA deputy commissioner under President George W. Bush, a Wall Street executive and a cancer survivor. The combination of experiences as a physician, patient, regulator, and executive provide an interesting backdrop to his mandate to implement the new administration's plan to cut regulation and speed up the approval process.

Gottlieb is well known as a proponent of deregulation of therapeutic products. He supports off-label marketing, and has stated that "FDA's caution is hazardous to our health," meaning that the agency's slow pace in drug approvals prevents patients from getting access to new drugs they desperately need, in part because the agency relies too heavily on "statistical results." Gottlieb has also stated that the advance of science is key to accelerating approval of needed drugs. He has stated that the "old paradigm" of seeking to approve a drug that treats a large population and is safe for that population is by necessity giving way to more patient-specific therapeutics, including treatments customized based on the patient's genetic information.

With his experience, Gottlieb well understands the scientific, medical and clinical disciplines, the critical

patient perspective, as well as FDA regulatory process. However, given his policy stance on the dangers of the FDA's current operational paradigms, it remains to be seen what changes Gottlieb will bring to the agency, including the interpretation and implementation of key legislation such as the Cures Act and the advancement of biosimilars through the BPCIA.

Litigation Developments: Amgen v. Sandoz

One week before the inauguration of the new administration, the Supreme Court granted certiorari in Amgen v. Sandoz to review the Federal Circuit decision holding that biosimilar applicants are not necessarily required to follow the BPCIA's "patent dance" procedure to resolve patent disputes over a biosimilar. More specifically, the questions presented are (1) whether the BPCIA provision stating that a biosimilar applicant "shall" provide the reference sponsor with its biosimilar application and manufacturing information is mandatory, and (2) if the applicant fails to provide that information whether the sponsor's sole recourse is to commence a declaratory judgment under a different section of the "patent dance" and/or a conventional infringement suit under the Patent Act. Sandoz argued that the patent dance is unnecessary, and the Federal Circuit agreed. A broad range of stakeholders in industry, government and academia have filed amicus briefs. The case is expected to proceed to oral argument in late April 2017, and a decision may be expected as soon as June 2017. The implications for industry cannot be overstated. Depending on whether a biosimilars applicant must provide the reference sponsor with its application and manufacturing information at the outset of the application process, the strategies for biosimilars developers, as well as reference license holders, may be significantly altered.

Business and Legal Considerations In the Biosimilars Field

The combination of so many ongoing, unresolved issues that could fundamentally affect how the BPCIA and related patent litigation may play out leaves many critical questions open for consideration. An interesting aspect of the biosimilars field, that adds another layer of complexity over existing uncertainty, is that unlike the traditional small molecule drug industry as it existed when Hatch-Waxman was enacted and developed, many companies in the industry are developing both biologics and biosimilars. In that climate, regulatory and legal strategies must be carefully developed, so as to minimize the risk of making law that could have adverse consequences. For example, in one recent biosimilar suit, the applicant attempted to fend off a declaratory judgment suit filed by the reference sponsor by rejecting the mandatory nature of the first step of the patent dance — the opposite position it took when fending off a previous biosimilar challenge to its own biologic.

Depending on the outcome of the Supreme Court decision, biosimilar companies may consider using more creative means to resolve patent issues. For example, the inter partes review (IPR) process in the patent office may serve as a strategy for clearing patents outside the "patent dance." However, under recent case law petitioning for an IPR may not provide biosimilar manufacturers with a reliable avenue for recourse. In January 2017, the Federal Circuit rejected the challenger's appeal of a decision of the Patent Trial and Appeal Board based on lack of standing. The appellate court held that Phigenix had no injury, as it had not been accused of infringement of the patent at issue. Thus, the alternative patent office process should be evaluated with caution.

Conclusion

We continue to await the outcome of a combination of critical issues that will determine the future of the BPCIA. It looks as though 2017 may be the most pivotal year yet for the BPCIA. We may finally see

relative consistency and certainty in the application of the BPCIA with the filing of more biosimilars applications. Thus, we may come closer to being able to answer the question whether the BPCIA can accomplish the goals of lowering drug prices without compromising patient safety.

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