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Recently Released FDA Guidance and Biosimilar Development: Implications for the Litigation Environment

By Genia Long and Carla Mulhern

Introduction

The Food and Drug Administration (FDA) in February released the first set of long-awaited guidance documents for the development of biosimilar versions of complex, biotechnology medicines under the Biologics Price Competition and Innovation Act (BCPIA). Europe has had a guidance based framework for biosimilars in place since 2005, and there are currently 13 biosimilars on the market there. Until now, however, no such guidelines had been released in the United States, and there have been no biosimilar approvals under the new law. The passage of BPCIA in 2010, the release of the first set of FDA guidelines, and the subsequent approval of biosimilar applications uner the new guidelines will usher in a new era for the global biotech industry.

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In light of these developments, drug manufacturers have been actively reconsidering and rebalancing their business portfolios. Attorneys and others engaged in intellectual property (IP) and antitrust litigation in the biopharmaceutical industry are also anticipating what these changes might mean for their "portfolios." In particular, there are important *product* differences between large-molecule drugs (biologics) and small-molecule drugs (pharmaceuticals), as well as differences between the *regulatory pathways* for biosimilars and small-molecule generics, each of which will have significant implications for IP and antitrust litigation.

An Overview of Product and Regulatory Differences

Product differences. Unlike small-molecule drugs, biologics are not manufactured through chemical synthesis but through carefully developed cultures of living cells. Because biologics are complex in structure, even small changes in the processes used to make them can significantly alter the safety and efficacy profile of the resulting products and present inadvertent immunogenicity issues. Additionally, biosimilars are more difficult to characterize completely using today's technologies. As a result, it is difficult for regulators to determine if they are similar enough to their reference products to be safely designated as "biosimilars" or "interchangeable biosimilars." Technological advances (which themselves may be proprietary and not generally available to potential biosimilar manufacturers) are improving the ability to fingerprint biologic drug substances; however, the manufacturing process remains a significant challenge to developing biosimilars, particularly for more complex biologic molecules, such as certain monoclonal antibodies. Companies may need to make significant investments in clinical trials, both to surmount regulatory approval requirements and to satisfy the needs of physicians, patients, and payers for market acceptance.

Another key product difference is that while generic drugs may be substituted for the reference brand by the pharmacist without the permission or direction of the physician (subject to state laws), biosimilars generally are not expected to be, at least initially. That is because regulators are expected to find them similar to rather than interchangeable with their reference products. In addition, biologics are likely to be injected or infused, often in specialist physicians' in offices, in clinics, or in hospital settings, and managed by payers as medical benefits, as opposed to being simple oral therapies, managed by payers as drug benefits.

As a result of all these factors, fewer biosimilar manufacturers are expected to enter the market; uptake is expected to be slower; and more limited price discounting is expected, compared with generic drugs.

Regulatory pathway differences. Besides product differences, there are important differences in the regulatory pathways for biosimilars and generic drugs. For example, under *BPCIA,* there is no "Orange Book" public patent-listing process for biosimilars. Instead, there is a new complex private disclosure process: Biosimilar applicants provide notice of their applications and share manufacturing information; reference-product identify their relevant patents, including product and process patents; and the parties negotiate, ultimately identifying a subset of patents for litigation. Additionally, under *BPCIA*, there is no automatic stay of biosimilar approval during the pendency of patent litigation, as there is for generics regulated under *Hatch-Waxman*. Rather, the biosimilar applicant must give the innovator 180 days notice of the first commercial marketing, during which time the innovator can seek a preliminary injunction.

Implications for the Litigation Environment

The distinct product characteristics of biosimilars and the differences between the *BPCIA* and generic pathway established under *Hatch-Waxman* likely will give rise to novel economic questions that will need to be addressed, as well as various changes in the litigation landscape.

A more "matrixed" IP environment. The development, production, and delivery of biologic drugs may rely on numerous patents on compounds, methods of use, and manufacturing processes. The modern biotechnology industry reflects a complex web of research, technology, and commercial relationships among "upstream" academic research institutions, small biotech start-ups, technology platform providers, "downstream" integrated biopharmaceutical firms and potential biosimilar manufacturers. This evolving industry structure means that marketed biotech products may be more challenging given this highly complex IP environment (with many patents, many stakeholders). In addition, the process may give rise to concerns that innovator firms will have access to a broad range of biosimilar competitors' IP.

Increased complexity in the analysis of patent infringement damages. The increased investments required and the slower market uptake associated with biosimilars relative to generics will have important implications for damages assessment in those IP cases where branded biologic manufacturers are claiming patent infringement and seeking lost profits. The current body of

economic research describing the effects of generic entry on market share and the pricing of branded products may be inapplicable in a number of situations. *De novo* economic analysis will be required. Meanwhile, in instances in which the remedy for infringement is limited to a reasonable royalty (such as in the case of untimely filed patent suits) the contributions of multiple IP holders to biosimilar products will raise the critical issue of "apportionment." Apportionment refers to the need to isolate the contribution of a particular patent of interest from overall product value. In contrast to small-molecule drugs, where there may be a single, controlling composition-of-matter patent, the typical biologic patent portfolio may involve many product, process, and method-of-use patents.

Antitrust concerns arising from product complexity and private disclosure process. The increased complexity of large-molecule biologics and the lack of transparency in the IP disclosure process specified under *BPCIA* may raise antitrust concerns, such as attempted monopolization, collusion, price-fixing, and patent misuse. For example, innovator firms may raise safety and efficacy concerns about a particular biosimilar product (perhaps through the FDA's citizens petition process) citing the complexity of biologics. Meanwhile, biosimilar manufacturers may claim these are "sham" petitions filed only to impede entry and reduce competition. The private information exchange associated with the IP disclosure process in the absence of the Orange Book may give rise to claims of collusion. Other actions could flow from the reimbursement procedures for biologics and the reliance on physicians to deliver these drugs, which may affect price competition and cost savings.

No automatic stay leads to increased emphasis on preliminary injunction. The absence of an automatic stay increases the likelihood that biosimilar applicants will introduce their products "at-risk"—meaning they may be launched before litigation issues have been resolved. The absence of an automatic stay also emphasizes the importance of motions for preliminary injunction, including an analysis of economic factors such as irreparable harm.

Conclusion

From both drug manufacturers' and litigators' perspectives, the FDA guidelines and subsequent approval of biosimilars in the U.S. will usher in a new era—one that will require careful strategic thinking and innovative economic modeling. The unique product and regulatory pathway characteristics that differentiate large-molecule from small-molecule drugs may create a need for rigorous economic analysis rather than a one-size-fits-all approach to addressing critical legal and strategy questions.