

# MARKET EXCLUSIVITY ISSUES FOR BIOLOGICS AND BIOSIMILARS



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Gregory Glover is an attorney and non-practicing physician who is one of the America's leading experts on the complex intersection between FDA regulations and intellectual property. Greg works with pharmaceutical companies and investors on strategic issues related to product life cycles. He has testified on behalf of the pharmaceutical industry before both houses of Congress, the FDA, the Federal Trade Commission, and the Department of Justice. Greg's expertise includes the patent and nonpatent market exclusivity provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), and analogous provisions of the Biologics Price Competition and Innovation Act (BPCIA). Greg's educational background includes receiving an M.D. from Duke Medical School, a J.D. (*cum laude*) from Harvard Law School, and an A.B. (*magna cum laude*) in Biochemical Sciences from Harvard College.

Biologics are large molecule medicines made from living cells through manufacturing processes that are far more complex and costly than manufacturing processes for small molecule drugs. Biosimilars are analogous to generic drugs for biologics, and are approved if they are shown to be "highly similar" to an already approved biologic drug (known as an innovator reference product). Although biosimilars do not have any clinically meaningful differences in safety or efficacy from their innovator, they are not truly bioidentical.

In the United States, Congress created the Biologics Price Competition and Innovation Act (BPCIA) with the intent to abbreviate the approval pathway for biosimilars in a way that is analogous to the abbreviated approvals for small molecules established in the Hatch-Waxman Act (HWA). Although the provisions for biosimilars are similar to the provisions in the HWA, they are not the same. The differences in legal and regulatory structure arise from the fundamental inability of biosimilar manufacturers to make an identical copy of the innovator. These differences have a substantial impact on biosimilar approval requirements, patent and regulatory exclusivity provisions, and market dynamics.

Although the FDA has provided guidance to address some aspects of biosimilar approvals, it has adopted a "totality of evidence" approach to provide flexibility in the requirements for specific biosimilar applications. Accordingly, the clinical testing needed to demonstrate that a biosimilar is "highly similar" to the innovator will be determined case-by-case.

BPCIA also provides a new approach to the patent and regulatory exclusivity provisions that govern the interaction of innovator and generic manufacturers in the HWA. For small molecules, the patent and regulatory issues are linked explicitly through provisions such as Orange Book patent listings and the 30-month stay of regulatory approval following the initiation of a patent infringement suit. There is no patent and regulatory linkage in BPCIA; regulatory approvals can proceed independently of any ongoing patent disputes. In lieu of the patent and regulatory linkage of the HWA, BPCIA provides for a highly complex patent information exchange process and related infringement litigation whose interpretation is still being disputed. In addition, the five-year (new chemical entity) and three-year (new product) exclusivities in the HWA have been replaced by a single 12-year reference product exclusivity in BPCIA. There is no independent exclusivity provided to the innovator for developing new indications/formulations. These differences in patent and regulatory exclusivity provisions will have a significant impact on product development strategies for biologics.

The market dynamics for biologics and biosimilars will also be different from brand-names and generics. When a generic enters the market, the price for the drug drops substantially because the market switches to the less expensive generic version. Rapid market penetration for the generic arises partly because pharmacists are allowed to substitute generics for brand-name drugs, and pharmacists get paid more to fill the generic. The significant drop in overall price translates into savings for the consumer, encouraging greater use of the generic. There may be greater than a 60% reduction in innovator use and consumer cost in the first six months. The picture is very different for biologics and biosimilars.

As mentioned above, biosimilars are "highly similar" -- but not identical -- to their innovators. As a result, physicians might be reluctant to switch to biosimilars, particularly because biosimilars are often used to treat life-threatening diseases. Some have also raised concerns about possible issues with immunogenicity that might not be apparent until several years of use.

Moreover, in order for pharmacists to substitute biosimilars for innovators, biosimilars must be given an additional designation as "interchangeable." None of the approved biosimilars have been shown to be interchangeable. In addition, most biosimilars are never even filled by a pharmacist, because they are administered in a hospital or by a healthcare provider. Accordingly, the rapid and robust uptake of generics to the market due to pharmacist incentives will not exist for biologics.

Finally, as described earlier, it is very difficult and costly to make biosimilars. Therefore, the price drop associated with a biosimilar coming onto the market will not be as significant as that for a generic small molecule. Nevertheless, the significant expense associated with some biologics might cause a physician's practice to consider the biosimilar, particularly for patients just starting treatment.

The differences in biosimilar approval requirements, patent and regulatory exclusivity issues, and market dynamics require innovator companies to adopt different strategies to manage the lifecycles of innovator biologics. Despite the uncertainties that remain, the biologics market for innovators and biosimilars will remain a significant source of growth for the pharmaceutical industry for the foreseeable future. The continued pursuit of innovative biologics and the development of the biosimilar market will produce a robust competitive market for large molecule drugs that is similar, but not the same as, the robust market between brand-name and generic small molecule medicines.