

## GENERIC VERSIONS OF BIOLOGICS: THE PROBLEM AND A POSSIBLE SOLUTION

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In 1984, Congress transformed the U.S. drug industry with the Hatch-Waxman Act. From that act, the generic drug industry and generic drugs evolved, ultimately saving consumers tens, if not hundreds, or billions of dollars. Nascent generic drug companies received a clear pathway to make and market generic drugs and traditional pharmaceutical companies received the promise of short-term market exclusivity and long-term extended patent protection. By most standards, the trade-off has worked well and relatively little legislative tinkering has been required since 1984.

Whether Hatch-Waxman, or some modified form of it works for newer "biologic" drugs is problematic, as is the part to be played by patents on such drugs. Conceivably, the problems involved in these two aspects of this important public policy issue may find a solution by a new approach, based on product by process patent claims.

Hatch-Waxman has been applied almost entirely to drugs characterized as small molecules. Typically, each such molecule comprises a well-defined combination of a relatively small number of atoms in a specific ratio and spatial relationship. Most drugs developed before 1990 and many since then meet this definition. The biotech industry has changed all that. Many, if not most, drugs developed since 1990 are large molecules, isolated from, or designed to mimic or interact with, native organic constituents in a patient's body. These drugs, known as biologics, are typically thousands of times larger, heavier and more complicated than small molecule drugs. Often, making the biologic drug involves growth or biological manipulation of another biologic molecule with unique biological tools.

Thus the rationale of Hatch-Waxman, which depends on the ease with which a well defined small molecule can be replicated, does not extend easily to biologic pharmaceuticals, which often defy definitive characterization. And yet practically all concerned parties agree with the public policy favoring the development of a scheme to permit the development of generic biologic drugs.

For the most part, there seems to be little disagreement that a follow-on biologic will almost never be identical to a prior approved drug. Follow-on biologics are therefore usually classified as biosimilar, as contrasted with bio-identical or bio-equivalent, the latter term being commonly applied to conventional drug follow-ons, which may be relatively freely substituted for the originals.

As with patent law reform generally, Congress has struggled, unsuccessfully to date, with proposed legislation to facilitate approval of follow-on biologic pharmaceuticals. The several follow-on biologic bills now pending in Congress confirm that Congress (or at least several significant members of Congress) does recognize that many aspects of Hatch-Waxman will not apply to biologic pharmaceuticals. The pending bills, however, differ in several ways which would dramatically impact the cost and effort required to secure follow-on approval. Among the differences: when data (as to safety and efficacy, for example) from a prior application may be used by a later applicant, the degree to which the follow-on applicant would be required to submit

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its own data on immunogenicity testing of the follow-on product irrespective of the immunogenicity data of an earlier applicant and most importantly, the extent to which clinical trials of a follow-on drug would be required, notwithstanding the clinical trials of an earlier biosimilar drug.

The European community leads the United States by several years in facing up to this problem and a number of biosimilar drugs have been approved in Europe. While a much smaller number of follow-on biologics have been approved in the U.S., the FDA has done so only by adapting regulations that had not been adopted with biologics in mind. For the most part, European legislation does not attempt to restrict how biosimilar biologics are approved but instead delegates the responsibility for drawing guidelines to an administrative agency, corresponding to the FDA, with express provisions giving much flexibility to the agency and requiring the agency to use the best science available, as it becomes available, to determine whether a follow-on biologic is in fact biosimilar to an earlier drug.

Among opinions expressed to Congress, research-based, or innovator, drug companies argue that giving that much flexibility to the FDA would permit inappropriate drug approvals and that the nature of biosimilars requires that high standards be a part of the governing legislation. From those representing the generic drug industry, Congress has heard that biologic follow-ons will be unduly hampered by statutory guidelines governing if and when a follow-on applicant must submit its own immunogenicity test results and/or clinical data.

A major difference between the various pending bills is the period during which, following approval of a new biologic drug, the data submitted for that approval would remain exclusive to the original applicant and unavailable to the follow-on applicant for the later application. In the pending bills, this period, referred to as the data exclusivity period, varies from zero to 14 years. The 14-year period is justified by economic studies which take into account the probability that any new drug candidate will eventually become commercial and the cost of bringing a new drug from initial identification to market. Fourteen years is the average break-even point, according to these studies, for the return from a new drug to equal its development cost. Those favoring no data exclusivity period contend that patent exclusivity provides all the protection needed to ensure a return on the research investment required to develop a new drug.

There are two problems with the latter view. First, current experience with Hatch-Waxman illustrates that when the timeline for drug development and regulatory approval are considered, 14 years of patent protection, following drug approval, requires an extension of the normal patent term. Hatch-Waxman provides for this and would presumably do so for biologic drugs as well. Whether that extension would be sufficient for biologics, given their more complex and therefore longer development period remains to be seen. A second, and more basic, problem flows from the uncertain nature of a biologic drug, because of its size, its complexity and the complexity of the manufacturing process by which it is produced. While any patent may be subject to attack, the protection provided by a patent based on an invention with this degree of complexity would be correspondingly uncertain.

Regardless of how Congress deals with this issue, the degree to which biosimilars are biosimilar will undoubtedly be left for debate with respect to each drug on an ad hoc basis. What remains is the open question of whether there can ever be a pathway which facilitates approval of a follow-on biologic which is not merely biosimilar to an approved drug but which is interchangeable with that drug. None of the pending legislative proposals necessarily provide such a pathway. Nor do the existing European regulations. Under the existing paradigm for non-biologics, the approval of

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interchangeable or substitutable generics is what permits consumers, and those sharing the burden of medical expenses, to save tens of billions of dollars.

Implicitly, and sometimes explicitly, those urging the uniqueness of biologics and the inapplicability of the existing paradigm to the approval of substitutable biologics contend that the only way to reliably make a biologic drug which is identical to an approved drug is by replicating the process by which that drug is manufactured. That includes replication of the starting point for the manufacturing process, which itself is typically a unique biological material.

This argument against the replicability of the drug, however, may be a boomerang for the innovator. A patent claiming the drug patent must necessarily enable others to replicate the drug. This suggests that the only valid way to claim such a drug may be a product by process claim. And if the biological starting material is not otherwise publicly available, a sample of it must be deposited in a public repository.

While Hatch-Waxman patent term extension may be useful for any patent covering any aspect of a drug, including for example, its formulation or its method of manufacture, an innovator typically chooses to extend the term of a patent which claims the active agent of the drug as a composition of matter. In the case of a biologic, the twin issues of replicability and enablement may force the innovator to rely on a product by process claim in order to validly cover the active agent as a composition of matter.

This presents an interesting possibility. Since the disclosure of a patent with product by process claims essentially guarantees replicability, the existence of such a patent may open a pathway to approval of substitutable biologic drugs. This may be the linchpin of Hatch-Waxman style auxiliary new drug applications for biologic drugs. Patent term extension of a product by process patent claim may then be the full equivalent of patent term extension of patent claims to small molecules typical of pre-biologic drug active agents. Indeed such an extension, if tacked onto the data exclusivity period of the biologic active agent rather than onto the original patent term, would fully protect the innovator for a period to justify its original investment. Other policy considerations may dictate the period to which the extension applies, but either way the public will have the benefit, at some relatively fixed point in time, of the generic substitutable drug.

Among other considerations, if this approach were to be adopted, is that of the protection accorded the original innovator if a latter innovator is able to replicate the drug by a different process. Presumably others will strive to do this, and may succeed. The question would be whether that latter innovator would be considered an infringer of the original innovator's patent claim. Present case law does not provide a clear answer to this question and a case now pending in the Court of Appeals for the Federal Circuit may provide an answer for product by process claims generally. Regardless of how that pending case is decided, the certainty of a legislative answer, as specifically applied to biologic drugs, may be a necessary adjunct of any follow-on biologics legislation which addresses the substitutability of biologic drugs with reference to product by process patent claims.

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