Abbreviated Approval of Generic Biologics

Access to Life-saving Medicine Bill Improves upon Current ANDA System

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The creation of an abbreviated approval pathway for generic biologics, like that existing for the approval of generic versions of traditional drugs, is at long last the subject of pending legislation—Rep. Henry Waxman’s recently proposed Access to Life-Saving Medicine Act. The legislation outlines, for the first time, a realistic and flexible framework for various levels of clinical trial interchangeability studies with tax credit incentives, shorter approval times, and limitations on the filing of patent lawsuits. It also preserves the critical period of exclusivity for the first interchangeable generic biologic approved.

The Drug Price Competition and Patent Term Restoration Act (a.k.a., the Hatch-Waxman Act) of 1984 originally established the framework for the approval of generic versions of branded drugs. The impetus for the Hatch-Waxman Act was the need to increase access to lower cost drugs to make them more affordable for patients and less of a drain on the public healthcare system. Generic drugs have been extremely successful in bringing down the high cost of prescription drugs and are currently estimated to save patients and payers $10 billion a year.

Approval Pathways

There are presently two abbreviated approval pathways under the Hatch-Waxman Act. One is section 505(j), which allows the submission of an Abbreviated New Drug Application (ANDA) for generic versions of branded drugs. The ANDA must establish that the generic version is the same as and bioequivalent to the branded drug, which may be done with limited clinical testing, after which, the applicant may rely on the FDA’s finding of safety and effectiveness for the branded drug. Once an ANDA is approved, the generic and branded drugs are treated as interchangeable, and a prescription written for the branded drug can be filled with the generic version.

The other abbreviated approval pathway, section 505(b)(2), is more flexible because it does not require bioequivalence to the branded drug. For example, the new version may have a different dosage or rate of absorption than the branded drug. Instead of requiring full preclinical and clinical testing, an applicant must submit testing only as to the differences. The applicant may otherwise rely on information from published scientific literature and on the FDA’s prior finding that the similar branded drug is safe and effective.

Depending on the substitutability rating it receives, an approved 505(b)(2) drug may be treated as interchangeable with the similar branded drug; if not, doctors must write a prescription specifically for the new version. The FDA has permitted very few well-characterized biologics to be regulated as drugs under Section 505(b). This limited group includes insulin, growth hormone, glucagon, calcitonin and hyaluronidase. For several reasons there currently exists no standard approval pathway for generic versions of more complex biologic therapeutics. Of primary concern in limiting the clinical trial requirements for any biologics are unanticipated immunogenic responses such as reactions to unique glycosylation patterns produced by different vector organisms.

Would-be generic biotech drug manufacturers cannot simply copy the original process or obtain vector samples for producing the biologic from the original drug application. This is so because, in addition to patent protection, the FDA permits drug manufacturers to maintain confidential business information, including trade secrets, within their drug applications, indefinitely. Therefore, long after the relevant patents have expired, the manufacturer of a biotech drug can continue to enjoy exclusivity pricing in the market. For each new generic version of a biologic, a complete, new application is currently required for FDA approval, which includes expensive preclinical and clinical testing proving the new version’s safety and effectiveness.

The Access to Life-saving Medicine Act. The legislation outlines, for the first time, a realistic and flexible framework for various levels of clinical trial interchangeability studies with tax credit incentives, shorter approval times, and limitations on the filing of patent lawsuits. It also preserves the critical period of exclusivity for the first interchangeable generic biologic approved.

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that the biologic is safe, pure, potent, and produced under good manufacturing practices. Biologics are typically 20 times more expensive per patient per day than a drug counterparty. The biologics market reached an estimated $32.8 billion in 2005 and as the fastest-growing sector of the prescription drug market, is predicted to exceed $60 billion by 2010.

The costs extend beyond individual patients, to insurance companies, health plan providers, and taxpayers. The same need for affordable healthcare that led to the 1984 Hatch-Waxman Act clearly favors the creation of an abbreviated approval pathway for follow-on biologics.

Rep. Henry Waxman’s Access to Life-Saving Medicine Act is the first proposed mechanism to allow the FDA to approve abbreviated applications for generic versions of biotech drugs without repeating expensive and duplicative clinical trials. It would bring desperately needed competition into the biopharmaceutical marketplace and put an end to indefinite monopolies.

Abbreviated Applications
The bill establishes a scientifically rigorous process for approval of generic versions of biotech drugs, authorizing the FDA to determine, on a product-by-product basis, what studies will be necessary to show that a new product is clinically comparable to the brand-name reference product. The bill also creates an improved process for ensuring that patent disputes are resolved early to avoid delays in competition caused by continuing patent litigation.

The bill amends section 351 of the Public Health Services Act to authorize the approval of abbreviated applications for biological products that are comparable to previously approved biological products. A comparable biological product applicant must demonstrate that there are no clinically meaningful differences between the two products. An applicant must also show that the new product shares the principal molecular structural features of the reference product and the same mechanism of action, if known.

The FDA would have the discretion to determine whether and what studies are necessary to establish comparability to the reference product and may require clinical studies. An applicant for a comparable biological product may elect, but is not required, to further establish interchangeability. The bill establishes tax credits for the cost of studies demonstrating interchangeability and grants the first applicant to obtain approval of an interchangeable version of a biological product a period of exclusive marketing during which no other interchangeable version of the product may be approved. The exclusivity period is generally a 180-day period similar to the current ANDA process, but the new bill permits more flexibility for delays due to pending litigation.

Applicants for comparable biological products may elect to ask the brand-name reference product manufacturer for a list of patents covering the product and may thereafter elect to notify the manufacturer that it has filed a comparable biological product application. If the applicant sends such a notice, it must contain a detailed statement explaining why the identified patent is invalid, unenforceable, or not infringed.

If the reference product holder fails to disclose a relevant patent, it may not later enforce that patent against that applicant. If no patent infringement action is brought within 45 days of notice of a challenge, the remedy in any later action to enforce the patent against that applicant is limited to a reasonable royalty.

Significantly, the legislation would also prohibit the reference drug company from rebranding authorized generics for sales, which weakens the financial incentives of market exclusivity for a generic producer under the current ANDA system. The legislation also prohibits frivolous Citizen’s Petitions made on behalf of the reference drug company seeking to unnecessarily delay the generic approval process.

In many ways, the proposed legislation not only provides a statutory vehicle for approval of generic biologics but also improves upon several areas of ongoing dispute in the current ANDA generic drug system. The Access to Life-Saving Medicine Act has been recently introduced and will likely not be debated until 2007 or later. Still, it provides an important long-awaited first step in establishing a regulatory process for addressing the growing cost of delivering biotech medicines.

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