

DEBATE OVER “GENERIC BIOLOGICS” POSES UNIQUE CHALLENGES FOR POLICY MAKERS

by

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Once again, the cost of pharmaceuticals is occupying the attention of the public, the press, and the U.S. Government. The politics of the situation are sufficiently strange that states are establishing websites which instruct their citizens on how to “re-import” prescription drugs from Canada, an act which is clearly illegal under current law and which Food and Drug Administration (FDA) Chief Counsel Dan Troy recently characterized as smuggling.

In 1984, Congress attempted a global settlement of the tension between the need to provide sufficient incentive to research-based companies to invest in the risky and expensive business of new drug development and the public’s desire for less expensive drugs with the passage of the Drug Price Competition and Patent Term Restoration Act of 1984, popularly known as Hatch-Waxman, after the principal Senate and House sponsors of the measure. Hatch-Waxman was a classic political compromise: the research-based companies gained back some of the patent life that lapsed while the FDA reviewed its products and the generic industry obtained what was thought at the time to be a clear path to market under specified conditions. (A simplistic definition of a generic drug is one which does not need to demonstrate that it is safe and effective for its intended use, that demonstration having been made by another party’s product.)

For many years, Hatch-Waxman seemed to be a compromise that worked reasonably well. New and profitable drugs continued to be invented, while off-patent drugs became the object of fierce price competition. As time passed, however, issues that appeared to have been resolved, and some which had not been considered in 1984, began to surface. When Congress passed the Medicare reform legislation late last year, it also attempted to resolve some of the most contentious remaining disputes. But Congress did not tackle what is arguably the largest unresolved issue between the research-based and the generic industries: whether or not generic, and presumably less expensive, biological products can reach the market, and, if so, under what rules. The financial and public health stakes are substantial: an estimated \$10 billion a year of patented biologics will lose patent protection in the next few years. And the increasing role of the Federal government in reimbursing for drug therapy can also be expected to intensify pressures for competition in a field where at least one life-saving biologic costs over \$150,000 a year for the patient’s entire life.

Biological products have required U.S. government approval for marketing for over a century, originally under the Biologics Control Act of 1902, later as part of the Public Health Service Act. Drugs, on the other hand, were not required to undergo premarket approval until the passage of the Federal Food, Drug,

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and Cosmetic Act (FD&C Act) in 1938. The definition of a biological product has not changed appreciably since 1902: “any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product ... or analogous product ... applicable to the prevention, treatment, or cure of diseases or injuries of man” To the public, these biologics are probably thought of as “drugs” despite the statutory difference. (To further confuse the matter, FDA has declared that products such as blood and blood derivatives also meet the definition of a drug and so are regulated as both drugs and biologics.) FDA did not regulate biologics until 1972, when it assumed that responsibility from the National Institutes of Health. And while FDA takes the position that a biologic can also be a drug and regulates both categories in essentially the same way, the statutes under which the two types of therapeutic agents are approved remain different. For many years, however, this difference was largely unimportant. The issue of what is a biologic assumed considerably greater importance with the advent of the “biotech revolution” and the dramatic increase in both the cost of development and the cost of purchasing biological products.

When Hatch-Waxman was enacted in 1984, Congress was persuaded that the new breed of biologics then under development were sufficiently challenging to produce, and the science sufficiently new, that they should not be subject to the same generic competition rules as drugs. Thus, Congress failed to create a path to market which did not require proof of safety and efficacy under the Public Health Service Act, as it did for drugs under the FD&C Act. But Congress was persuaded that the fruits of the biotech revolution should receive the same patent term extension as it provided for drugs under the FD&C Act. Thus, one could argue that biologics get to play the tune without paying the piper: they enjoy patent term extension but do not face the prospect of generic competition when patents expire. This result produced generally little comment in 1984 as there were few, if any, companies interested in or capable of producing generic biologics. Twenty years later, the generic drug industry is significantly more sophisticated and the number of profitable biotech drugs on the market has not escaped notice.

The Generic Pharmaceutical Association (GPhA) has made the availability of generic biologics one of its top priorities of 2004. The Biotechnology Industry Organization (BIO), on behalf of the research biotech-based industry, is equally committed to preventing the appearance of generic biologics.

FDA, for its part, has said that it hopes to have a “structure” for generic biologics ready for congressional consideration in early 2005. But FDA has also noted that some biologics, through a quirk of administrative history, have actually been approved as drugs under the FD&C Act and thus arguably require no additional legislation for FDA to approve generics if the science justifies it.

In a Citizen Petition filed with FDA in April, 2003, BIO set forth a number of reasons why it believed that neither science nor law permitted FDA to approve biologics for which the full complement of safety and efficacy studies have not been performed. The petition asked that FDA:

- “Conduct a meaningful public participation process” on the FDA’s policies concerning approval of new drugs under section 505(b)(2) of the FD&C Act;
- Refrain from approving “under any statute it administers” any application for a therapeutic protein that does not contain the full complement of non-clinical and clinical studies required for approval of an original application;
- Withdraw its 1999 draft guidance on applications covered by Section 505(b)(2).

BIO’s petition seeks to deflect any effort by FDA to approve therapeutic proteins, such as insulin and recombinant insulin, under the provisions of section 505(b)(2) of the FD&C Act. As BIO clearly recognizes, these products are in the most immediate danger, because they were in fact approved as drugs rather than as biologics, and thus, at least arguably, eligible for generic competition.

BIO’s argument cannot fully be understood without some background on FDA’s tortured attempts to create pathways for generic drugs to enter the market. The FD&C Act has always required that “new” drugs receive FDA permission for marketing. From passage of the Act in 1938 until 1962, that permission was

based largely on evidence of safety. Indeed, it was not uncommon in the 1940's and 1950's for subsequent applicants to market a drug already approved by FDA to receive a letter stating that the agency no longer considered the drug "new" and that premarket approval was therefore no longer required. When Congress enacted the Drug Amendments of 1962, it for the first time required that new drugs also present evidence of effectiveness to FDA for approval. The legislative requirement for clinical trials to demonstrate effectiveness began the long and steady climb in the cost of new drug development. Yet one of the most significant changes wrought by the 1962 Drug Amendments was created by FDA, not by Congress. FDA recognized that the effectiveness requirement substantially increased drug development costs. At the same time, FDA was increasingly leery of declaring drugs to be not "new" and thus not subject to premarket approval and the increased regulatory oversight that accompanies that designation. The agency response to these changes was to essentially hold that there could be no generic copies of post-1962 new drugs. While a patent expired in 17 years (since extended to 20), an approved NDA could last, in theory, forever. By the 1970's, when there began to be efforts to moderate drug prices, FDA began to examine ways to get around the stranglehold it had itself created.

One of the mechanisms FDA developed was the "Paper NDA," a new drug application which, in theory, was supported in its entirety by published literature about the drug. This was one scene in the battle that ended with passage of Hatch-Waxman in 1984. In new section 505(j) of the FD&C Act, Hatch-Waxman created a relatively simple path to market for generic copies of drugs which were no longer covered by patents nor various statutory exclusivities: the sponsor basically had to show that it could manufacture the drug in accordance with current good manufacturing practices and that the drug was "bioequivalent" to the pioneer drug. Congress also created another path to market for non-pioneer drugs: the so-called 505(j)(2) process. This provision permits an applicant to both rely upon FDA's prior approval of a pioneer drug, as well as conduct clinical or other studies to support differences between the pioneer and the copy, differences not permitted under Section 505(j). Industry and FDA disagree whether or not section 505(b)(2) was simply a codification of the prior Paper NDA process or an expansion of it.

FDA has interpreted Section 505(b)(2) as authorizing it to rely on a previous finding of safety and efficacy, as it does in approving a generic drug under section 505(j), while at the same time requiring additional studies to demonstrate safety and/or effectiveness of a new dosage form or new combination of active ingredients. It is FDA's suggestion that 505(b)(2) might provide the legal basis for approval of substantial copies of biologics regulated as drugs which has posed the most immediate threat to BIO. In a letter dated October 14, 2003, FDA denied those portions of BIO's petition, as well as similar petitions filed by others, which challenged its authority to use Section 505(b)(2) to approve generic biologics. FDA noted that BIO's petition also stated "scientific and technical arguments as to why biologically derived products, in particular, are not suited for approval under section 505(b)(2). Those arguments, FDA said, would be addressed "in a response to be issued later." "Later" has yet to arrive.

BIO's scientific argument is relatively straight-forward:

- Biotechnology products include complex substances that are produced using living organisms for therapeutic use. . . . Approval of follow-on biotechnology products must be based on the same rigorous standards applied by the FDA for the approval of pioneer biotechnology products. Patients should not have to accept greater risks or uncertainties in using a follow-on product than when they use an innovator's product.
- Currently, the science does not exist to provide an alternative to a full complement of data, including clinical evidence, to demonstrate safety and effectiveness for follow-on biotechnology products. As FDA has frequently acknowledged, biotechnology products can be difficult to fully characterize. Also, due to differences in the composition of a biotechnology product or differences in how the product is manufactured, different versions of the same biotechnology product produced by companies other than the innovator will inevitably differ in certain respects from the innovator product. Experience shows that even small product differences can result in significant safety or efficacy differences. Therefore, in the current state of scientific knowledge and technique, a clinical

trial remains a fundamental principle for evaluating the safety and effectiveness of a follow-on biotechnology product.¹

Requiring the “full complement of data, including clinical evidence,” means that there is little or no likelihood that generic biologics would emerge.

The generic industry, of course, views things differently. On the legal arguments about section 505(b)(2), its arguments track those made by FDA in denying the BIO petition. GPhA also believes that there are sound public policy reasons for encouraging generic biologics:

- Research and development of pharmaceuticals is a public-private partnership, with taxpayers paying for much of the basic research leading to successful biological products;
- The socioeconomic factors are the same as those already decided by Congress in enacting Hatch-Waxman;
- Single source drugs increase the likelihood of shortages, especially in an era of heightened national security;
- The science exists today for generic copies of at least some well characterized biologics.
- FDA has already approved without requiring clinical trials the kinds of manufacturer-requested production changes which BIO claims are required in order to approve generic copies.

GPhA does agree with BIO that legislation is needed to permit the broad range of biologics to be available for generic competition. In addition, it also does not argue that a system for generic biologics can be as simple as that which has evolved for generic drugs. GPhA believes that:

- With appropriate knowledge of a given molecule, an equivalent can be made that is therapeutically interchangeable and safe;
- Requirements to show equivalence and safety should be defined by FDA on a case-by-case basis;
- The product involved and the state of the science should drive the system.

No interest wants to expose American patients to drugs or biologics which are unsafe or ineffective. And controlling health care costs is a poor argument for cutting corners. Yet many of the scientific arguments advanced by BIO reflect similar arguments advanced by the research-based drug industry in 1984. On the other hand, there are still drugs subject to Hatch-Waxman for which FDA will not approve generic copies because it cannot be shown that the copies are bioequivalent to the original drugs. While the public debate centers on whether the science exists to make reasonable conclusions about safety and efficacy in the absence of clinical trials, the economic impact of any decision, or no decision, is enormous, and will inevitably influence the final outcome. Indeed, while the debate over generic biologics seems to be on hold until sometime next year, it is likely that this reprieve exists because of the current battle over reimportation of prescription drugs, another battle involving significant issues of public health and money.

¹An interesting historical footnote to BIO’s position is presented by the regulation of antibiotics. Developed in the 1940’s and rigidly controlled by FDA during World War II, antibiotics were produced by a fermentation process which also made it difficult to characterize them precisely. As such, every batch of an antibiotic produced was subject to FDA review before release to the public, a requirement that was not finally ended until passage of the Food and Drug Administration Modernization Act of 1997.