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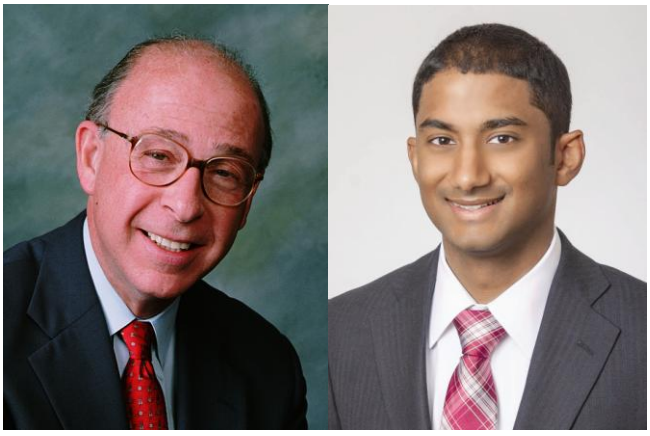
Generic Drugs At 30: Fulfilling The Promise And Path Ahead



Law360, New York (July 24, 2014, 8:13 AM ET) -- In the quest to reduce health care costs and to provide affordable medical care to patients, few events have been as significant as President Ronald Reagan signing into law the Hatch-Waxman Amendments to the Food, Drug and Cosmetic Act. Formally known as the Drug Price Competition and Patent Term Restoration Act, this watershed moment on Sept. 24, 1984, ushered in a new paradigm in the availability and use of prescription medicines in the United States. Seniors and others on fixed incomes were now able to afford needed drugs, and strict regulatory requirements guaranteed that those drugs were the bioequivalent counterparts of more expensive branded alternatives. Generic drug manufacturers, freed of having to perform lengthy, expensive clinical trials replicating those of brand drug manufacturers, and utilizing streamlined Abbreviated New Drug Application procedures, were encouraged by the prospect of a shorter pathway to the marketplace. Physicians, too, recognized that generic medicines offered all patients, regardless of income or wealth, the finest pharmacotherapies available. In the 30 years since that pivotal event, how far have generics come, and what are the challenges which lay ahead?

Before addressing the challenges, let's consider how widely accepted generic drugs have become. As of the end of last year, published data demonstrates that generic competition generated U.S. prescription drug savings in excess of one trillion dollars between 2003 and 2012.[1] Generics today, more than 86 percent of prescriptions written, account for 29 percent of total drug sales in the U.S.[2] The country is the largest of the top five generic markets by value, accounting for 46.9 percent of the $117 billion global total, and, by volume, the U.S. generic market comprises 22.7 percent of the global figure of 700 billion units.[3] From a marketplace standpoint, therefore, it is hard to argue with the entrenched success of generic medicines in America. With more than half of medications available to patients at a cost of five dollars or less[4], and almost 80 percent of all prescription drugs marketed in the U.S. having a generic counterpart[5], Hatch-Waxman's extraordinary benefit to consumers cannot be seriously doubted.

Notwithstanding these successes, several significant challenges remain for generics.

Generic Drug Labeling

Last September, the U.S. Food and Drug Administration announced its promulgation of new drug labeling rules for generics. In large part, this was in response to the U.S. Supreme Court's seminal generic drug federal preemption decisions, PLIVA Inc. v. Mensing[6] and Mutual Pharm. Co. v. Bartlett[7]. In those cases, the court concluded that generic drugs were required by Hatch-Waxman and the FDA's own regulatory scheme to remain "the same as" their brand drug counterparts in their label warnings and design. Unlike brand drug companies, the court found, generics under existing regulations and legislation were unable to initiate or implement changes in their drugs' label warnings, and the requirement of bioequivalency precluded any material variations in the "design" of generic medicines. As a result of Mensing and Bartlett, countless pending and later filed products liability actions against generics were dismissed notwithstanding considerable but ultimately unsuccessful efforts by plaintiffs' counsel to plead surviving claims.

Recently, the FDA announced that its new generic drug labeling rules will be unveiled in December.[8] Under the draft rules published for comment[9], all drug manufacturers — brand and generic — would continue to monitor, collect and report adverse drug experiences, but now both could propose revisions to product labeling based on newly acquired safety information. As commentators have noted, however, with multiple manufacturers often in the marketplace with the same drug, there is the potential for confusion among prescribing physicians as differing label changes are suggested to the FDA, and, contemporaneously under the proposed rules, disseminated to physicians. Although the FDA will ultimately decide whether to approve each proposed label change or not, it has acknowledged "concerns about temporary differences in safety-related labeling." Whether these regulatory changes, if adopted, will promote or undercut labeling uniformity, whether the cost to generics of compliance would increase the cost of drugs to consumers, and whether generics may opt to abstain from producing certain medications altogether because of perceived increased liability risks, currently are unresolved issues.

Patent Litigation Settlements

Few subjects have been as vexing for both brand companies and generics as determining an appropriate framework for the settlement of patent litigation instituted because of a generic's challenge to the validity and preclusive scope of the innovator's patents. Prior to last year's Supreme Court decision in Federal Trade Commission v. Actavis Inc.[10], involving the testosterone drug AndroGel, courts were sharply divided on the antitrust implications of such patent settlement agreements, especially those under which the generic postponed its market entry in exchange for a "reverse royalty" or other payments from the innovator company. Congress, in several false starts, likewise failed to conclusively resolve the issue.

The generic drug industry supported such settlements as pro-consumer by permitting generic competition sooner than if these cases — expensive, time-consuming and complex — were taken through trial. The Federal Trade Commission, often divided on the competitive impact of drug patent settlement agreements, conceded that not all contained what it termed "pay-for-delay" provisions, only about a third did.

The Supreme Court, considering these issues in the AndroGel case, held that such settlements, contrary to the position espoused by the FTC before the Court, were not presumptively anti-competitive, and that

each case required a case-by-case assessment under a "rule of reason" antitrust analysis. The practical impact of the court's decision remains unclear, and numerous challenges by the FTC and private parties to patent settlements have followed. Lower courts are now addressing these issues; and new judicial guidelines are likely as drug companies seek the correct balance and structure in resolving their patent disputes. Among the features of patent settlements now under review in the courts, in addition to cash payments to generics by the innovator, are provisions limiting the innovator from authorizing other generics to enter the marketplace to compete with the generic first-filer (which is entitled to a 180-day market exclusivity period), and nonmonetary benefits provided by the innovator to the generic manufacturer.

Quicker Access to the Marketplace Under GDUFA

Hatch-Waxman's passage signaled the start of a new and distinct regulatory regime at the FDA for the intake, processing and approval of thousands of Abbreviated New Drug Applications ("ANDAs") received from generics. With its staff overwhelmed, the FDA's ANDA backlog expanded exponentially. Recognizing the necessity of devoting considerably greater resources to satisfy Hatch-Waxman's promise of an increased formulary of affordable drugs available to U.S. consumers, the FDA partnered with industry and Congress in the enactment of the Generic Drug User Fee Amendments of 2012, GDUFA, which parallels similar legislation affecting brand drug prescription pharmaceuticals. Under GDUFA, generics pay user fees to the FDA to supplement the costs of reviewing generic drug applications and inspecting facilities. GDUFA's primary objectives were to clear a backlog of over 3,000 ANDAs pending approval, to reduce ANDA approval time from an average of 32 months to 10 months within five years and to achieve parity in domestic and foreign generic drug plant inspections.

As noted in a 12-month progress report tracking the review and processing of the ANDA backlog[11], the FDA reported a reduction in the backlog of 30 percent with the issuance of so-called "first action" letters denoting, for instance, ANDA approval or tentative approval, issuance of a complete response letter (documenting major and minor deficiencies in the submission), a rejection of the submission or its withdrawal. Complicating this process was the agency's receipt in the interim of more new ANDAs and Drug Master File submissions than it had previously anticipated.

Working with industry to improve the quality of ANDA applications, which would facilitate their review by agency personnel, the FDA seeks by GDUFA's third year to achieve metrics meaningfully disposing of the ANDA backlog and materially shortening review times. Whether these goals will be achieved is dependent in large part on the commitment of significant resources, especially the hiring of competent FDA staff dedicated to implementing this program, and improving the channels of communication between agency personnel and ANDA sponsors.

Access to Brand Drugs for Bioequivalency Testing

For years, in assembling data for ANDAs, generics frequently had difficulty in obtaining from brand drug companies samples of their drugs for bioequivalency tests. Generics seek these samples to perform required bench tests and limited clinical trials on human subjects demonstrating that the generic drug is bioequivalent to the brand in its composition, effectiveness and adverse event risk profile. Over the past few years, and facing continued resistance by certain brand drug manufacturers, generics sued them, challenging claims by the innovator that supplying drug samples would contravene the strictures of the Risk Evaluation and Mitigation Strategy ("REMS") program in place for the drug. While most of these suits have settled on confidential terms, they have garnered the attention of the Federal Trade Commission and the FDA, both of which have clarified that REMS programs are not compromised by providing brand

name drugs to generics for bioequivalency testing under appropriate safeguards and protocols. Indeed, the FTC opined as amicus in one such case that withholding drugs for this purpose could violate the antitrust laws by impeding and blocking generic competition.[12]

Generics are hopeful that such expressions of support by two top federal agencies will open the door to securing needed brand drug samples for bioequivalency tests under proper safety measures ensuring REMS compliance as to those drugs with such a program in place.

Attaining cGMP Compliance

Utilizing the approximately $300 million a year which the FDA receives from generics in user fees, the agency is intent upon narrowing the gap in the frequency of domestic and foreign drug plant inspections. In February, FDA Commissioner Dr. Margaret Hamburg concluded an historic visit to India, a visit intended to reinforce the agency's regulatory requirements, especially its cGMP (current Good Manufacturing Practices) standards. Although most generics here and abroad are in compliance with these standards, FDA drug plant inspections in recent years have resulted in renewed efforts by generics to achieve cGMP benchmarks satisfying the high testing and product quality requirements demanded by the FDA for finished products marketed in the U.S.

Conclusion

Editorial constraints preclude the detailed consideration of other issues of current importance to generics in their expanding businesses. Among them is the current status of biosimilars, living cell-based equivalents of biologic drugs. In the years following enactment of the 2009 Biologics Price Competition and Innovation Act, the pathway for generic biosimilar drugs has not been fully defined by the FDA notwithstanding the issuance of guidance documents and a continuing dialogue between the industry and the agency. Many generics, nevertheless, are intent on pursuing these higher profit, more complex medicines to compete against brand name biologics and make these important medications more widely available to patients at a lower cost. A related topic of interest to generics is the continuing lobbying campaign by brand pharma and its allies at the state level to establish legislative barriers to the prescription and use of generic biosimilars. These efforts have led to mixed results thus far, with most states rejecting such legislation.

As an alternative to ANDA Paragraph IV litigation, generics also have been exploring the use of inter partes review ("IPR") procedures before the Patent Trial and Appeal Board for the resolution of patent disputes between brand and generic manufacturers. IPR, operating under new procedures put in place by the 2012 America Invents Act, likely will demonstrate greater efficiency, significant cost savings and prompter results than in court cases.

Although challenges remain for generics, it is clear at the 30-year mark that the promise of Hatch-Waxman has been realized, quite possibly beyond the dreams of Senator Orrin Hatch and Congressman Henry Waxman. Access to affordable generic drugs by all Americans has dramatically increased, product safety and effectiveness has been conclusively affirmed by both patients and their prescribing physicians, and the generic drug industry has demonstrated time and again its ability to influence and shape public health care policy.

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[1] GENERIC PHARM. ASS'N, GENERIC DRUC SAVINGS IN THE U.S. 1 (5th ed. 2013); see also U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-12-371R, DRUG PRICING: RESEARCH ON SAVINGS FROM GENERIC DRUG USE 9-11 (2012).

[2] See IMS INST. FOR HEALTHCARE INFORMATICS, MEDICINE USE AND SHIFTING COSTS OF HEALTHCARE: A REVIEW OF THE USE OF MEDICINES IN THE UNITED STATES IN 2013 40, 51 (2014).

[3] Global market tops US$117bn, GENERICS BULLETIN, May 2, 2014, at 8.

[4] See IMS INST. FOR HEALTHCARE INFORMATICS, supra note 2, at 14.

[5] See WENDY H. SHACHT & JOHN R. THOMAS, CONG. RESEARCH SERV., R41114, THE HATCH-WAXMAN ACT: OVER A QUARTER CENTURY LATER, at i (2012).

[6] 131 S. Ct. 2567 (2011).

[7] 133 S. Ct. 2466 (2013).

[8] Semiregulatory Annual Agenda, 79 Fed. Reg. 34,051 (June 13, 2014).

[9] Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, 78 Fed. Reg. 67,985 (proposed Nov. 13, 2013).

[10] 133 S. Ct. 2223 (2013).

[11] FDA, FY 2013 GDUFA PERFORMANCE REPORT (2014).

[12] FTC's Brief as Amicus Curiae, Mylan Pharma., Inc. v. Celgene Corp., No. 2:14-cv-02094 (D.N.J. filed June 17, 2014).
