



The Ongoing Regulation of Generic Drugs

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Today, generic drugs account for 63% of all U.S. prescriptions for drugs (see Figure 1). Since generic drugs sell at substantially lower prices than their brand-name counterparts, they save consumers

and purchasers of prescription drugs tens of billions of dollars per year. Moreover, their expanded role has been linked to an attenuation of overall price increases for prescription drugs. Between 2007 and 2010, roughly 110 drugs will lose their patent protection — including well-known products such as Norvasc (amlodipine), Imitrex (sumatriptan), Fosamax (alendronate), and Risperdal (risperidone). Estimates suggest that these 110 drugs are currently responsible for \$50 billion a year in sales¹ — so competition from generic drugs could generate large additional savings.

These economic benefits are widely viewed as a health policy

success story made possible by the Drug Price Competition and Patent Restoration Act of 1984, or the Hatch–Waxman Act, which set the rules under which generic pharmaceutical products could compete with brand-name products. In 1984, only 18.6% of U.S. prescriptions were written for generic products. The Hatch–Waxman Act aimed to inject price competition into the prescription-drug market while honoring legitimate claims to intellectual property rights by brand-name–drug manufacturers that invested large sums in research and development.

Price competition from low-cost imitators threatens the profits of brand-name manufacturers and

reduces their returns on innovative activity, spurring them into actions that may blunt the impact of competition. Price competition also limits the profits of generic-drug manufacturers (see Figure 2) and leads them to seek ways of insulating themselves from intense rivalry. Market participants have responded to the regulatory rules in ways that serve their own interests, so Congress has continually reassessed the regulations and sometimes altered the rules to better achieve the law's original aims.

Before 1984, generic-drug makers were obliged to conduct the same safety and efficacy tests that had been required of the original brand-name manufacturers to receive Food and Drug Administration (FDA) approval for marketing. These provisions often rendered it noneconomical to bring a generic to market. The Hatch–Wax-

man Act changed all that. It contained three features that affect competition between brand-name and generic drugs.

Most significantly, the law set out an abbreviated process for generic drugs to receive FDA approval. Generic-drug manufacturers must establish bioequivalence to the active ingredients of the original drug and demonstrate adherence to FDA-approved manufacturing processes. This provision obviated the necessity of conducting clinical trials. Second, the law allows generic-drug manufacturers to apply for FDA approval and conduct tests of bioequivalence before the relevant patents expire — without being subject to patent-infringement claims. Finally, it specifies a process for the resolution of patent disputes between generics firms and brand-name firms.

Several aspects of this third provision are especially important. Generics manufacturers are re-

warded for successfully challenging a patent: the first firm that files an Abbreviated New Drug Application is granted a 180-day period of exclusive marketing among generic products. Generics firms that challenge a patent are required to claim that their product will not infringe on any existing patents. But if a patent-infringement action is initiated by a brand-name manufacturer within 45 days of the noninfringement claim, the FDA cannot approve a generic product for 30 months or until the litigation is resolved.

The incentives created by these provisions have had profound effects on the market: today's generics industry has annual sales of about \$35 billion.² But the law has also had some troubling repercussions.

First, it has resulted in a great deal of litigation — some reflecting reasonable disagreements over the boundaries established by patents, some merely representing a

profitable tactic whereby brand-name manufacturers can delay the entry of competitors. Consider the financial consequences of a 30-month delay in the release of a generic drug that would compete with a brand-name drug that earns \$1 billion per year and costs a few cents per pill to manufacture. In 2003, Congress acted to limit this type of litigation by constraining the number of such suits that a manufacturer could bring in relation to a particular product. Nevertheless, to shield themselves against competition, manufacturers now carry an average of 10 patents for each drug — as compared with an average of 2 a decade ago.

There is also intense price competition among generic products. Generic-drug manufacturers have sought ways of gaining some competitive advantage over their rivals so as to be able to raise prices. One approach was to forge exclusive relationships with producers

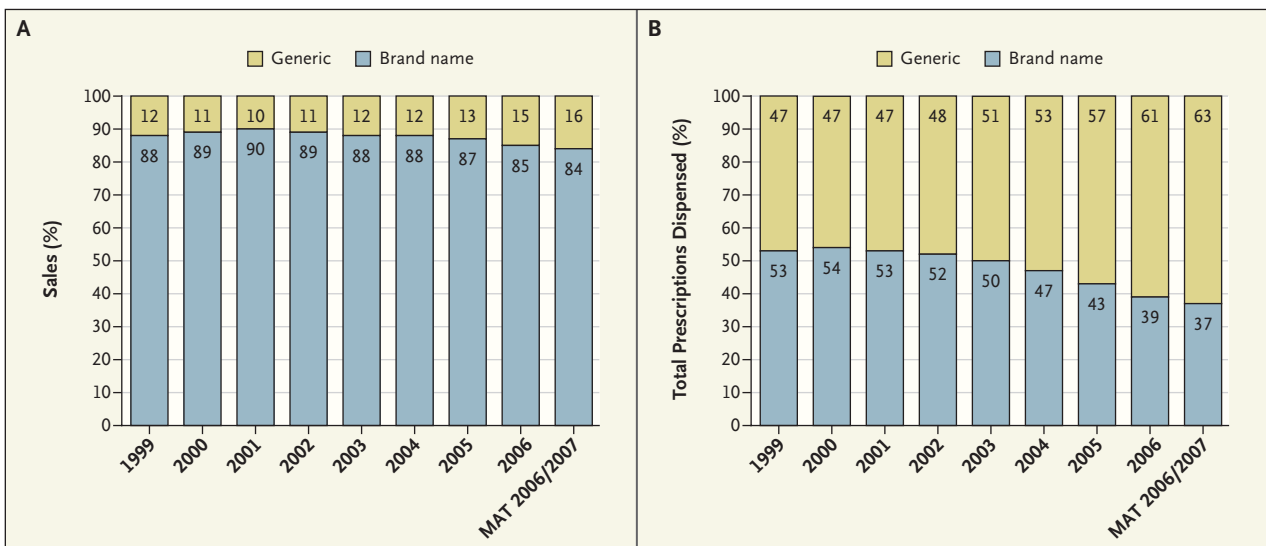


Figure 1. Proportions of Total Expenditures on Prescription Drugs (Panel A) and of Total Prescriptions Dispensed (Panel B) Accounted for by Brand-Name Drugs and by Generic Drugs.

MAT denotes moving annual total; MAT 06/07 represents the 12 months ending in June 2007. Data are from IMS Health, National Prescription Audit Plans, National Sales Perspective, June 2007.

of a drug's active ingredients, preventing rivals from being able to supply the market. These arrangements were found by the Federal Trade Commission (FTC) to violate antitrust law,³ and antitrust authorities continue to monitor the conduct of generic-drug manufacturers closely.

Makers of brand-name drugs have reacted to the prospect of patent expirations by creating reformulations of key products that use a different delivery system and can therefore be patented. Examples include long-acting versions of a drug or versions that do not require the user to swallow a pill. Brand-name drug companies commonly introduce such products before the patent on the original drug expires, with the goal of inducing some users to switch to a product with a longer-running patent.

Brand-name firms have also held on to some revenue streams by launching their own "authorized generic" around the time when another generic version enters the market, usually through a

licensing arrangement with a generic-drug manufacturer. These products are often launched in cases in which a generics firm has successfully challenged a patent. Examples have included authorized-generic Allegra (fexofenadine), Zithromax (azithromycin), and Pravachol (pravastatin), each of which claimed 30 to 50% of generic-drug sales. The authorized generic drug competes with the generic drug that was entitled to a period of market exclusivity, but since the original manufacturer is licensing the right to produce its own drug, it is permitted to sell a generic form. Such a move gains revenue for the brand-name manufacturer and undermines the financial benefits of the 180 days of exclusivity granted to the generic-drug firm that challenged the patent — reducing the payoff for firms that challenge patents and thereby discouraging such challenges.

In addition, some manufacturers have entered into arrangements whereby a generic-drug company agrees to delay market entry in

exchange for a payment that settles its patent litigation. Such settlements occurred for K-Dur (potassium chloride), Cardizem (diltiazem), and Nolvadex (tamoxifen), among other drugs. These settlements have been fiercely contested by the FTC and health care payers as anticompetitive. Court judgments have been mixed, but an appeals court recently ruled that such agreements were legal. The final word will probably eventually come from the Supreme Court.

Moreover, in some cases, brand-name companies may find their own patented drugs competing with generic versions of rival drugs in the same class. These companies have powerful incentives to devise ways to stem revenue losses long before their own patents expire. Companies facing such threats to revenues will institute measures aimed at differentiating their products, in the minds of doctors and patients, from those of rivals. A brand-name manufacturer seeking to show a meaningful clinical advantage of its own product will mount promotional campaigns reporting research that tries to persuade physicians and patients to continue purchasing its product. A recent case in point is the Pfizer campaign to promote the clinical advantage of the statin Lipitor (atorvastatin) over a generic rival.

Thus, manufacturers of both brand-name and generic drugs have responded to the provisions of the Hatch–Waxman Act in ways that advance their own economic interests. This is exactly what policymakers should have expected to happen. The impact of public policy is always complex. In the larger context of Hatch–Waxman, some

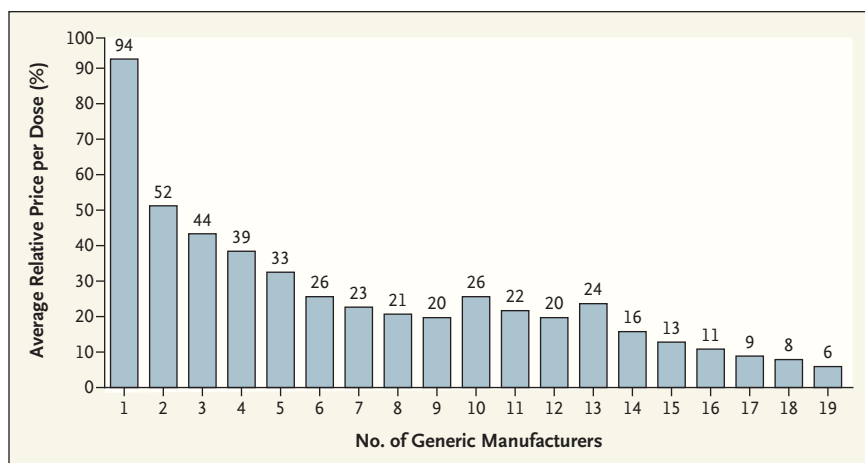


Figure 2. Change in the Average Relative Price of a Drug as the Number of Generic Versions Increases.

The average relative price is the average price of a generic version divided by the price of the brand-name drug. Data are from an FDA analysis of retail sales data from IMS Health.

effects that are considered socially undesirable, such as a manufacturer's development of a new formulation of a product to extend patent life, can be seen as one cost that is incurred to collect the very large benefits of the law. The policy question then becomes what the net benefits of addressing the legislation's side effects might be.

Recent congressional debates have focused on regulating author-

ized generic drugs and limiting the ability of brand-name manufacturers to settle patent litigation through payments to generic manufacturers. In these cases, Congress seems to be directing its attention sensibly to areas in which modification of the law may reduce problematic conduct without undermining the law's benefits.

An interview with Dr. Frank can be heard at www.nejm.org.

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Closing the Affordability Gap for Drugs in Low-Income Countries

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The cost of treating human immunodeficiency virus (HIV) infection is decreasing. Nonetheless, tenofovir–emtricitabine–efavirenz, the standard first-line treatment in North America and Europe, is prescribed rarely in low- and middle-income countries. The lowest annual cost for a generic formulation of this regimen is still hundreds of dollars more than the \$100 annual cost of generic stavudine–lamivudine–nevirapine, an effective but less safe alternative that has been largely abandoned in Western countries (see Figure 1).¹

Unfortunately, many medications remain unaffordable in low- and middle-income countries. In the public sector, medicines are often provided free of charge, but essential drugs may be unavailable.² If they were less expensive, governments could provide them to more patients and international drug aid would benefit more people. In the private sector, medicines are more available but not more affordable. One

way to estimate affordability is to calculate the number of days the lowest-paid government employee would have to work to purchase a 1-month treatment regimen.² The affordability of standard treatment for coronary heart disease in the private sector varies from less than 2 days' wages in Bangladesh and Sri Lanka to about 5 in Brazil, Nepal, and Pakistan to more than 18 in Malawi (see Figure 2). The affordability range of standard asthma and diabetes treatments is similar.³

Medicines may be unavailable because of bureaucratic factors that delay licensure and discourage manufacturers from introducing drugs into low-income countries. Manufacturers' prices are an important cause of unaffordability, but there are many other factors, including import tariffs and taxes, distribution costs, a lack of comparative price data, and markups by distributors, pharmacies, and doctors who dispense medications.

The affordability of generic

drugs may be improved by increasing the efficiency and volume of production, prescribing the lowest effective dose, clarifying treatment guidelines so that manufacturers can focus on fewer drugs, stimulating competition, negotiating with manufacturers, and publicizing the lowest prices.¹ However, it may take years to streamline production and maximize volume-related efficiencies. Without robust competition, generic manufacture does not lead to the lowest prices; retail prices may dwarf production costs. A credible threat of government action may also encourage price reductions.

Drug companies have issued nonexclusive licenses for manufacturers to produce generic versions of patented medicines for sale in low-income countries and have established differential pricing for countries of various income levels. Voluntary licenses, however, may limit the countries in which the drugs can be sold and impose conditions that some