

Balancing Innovation and Access: Patent Challenges Tip the Scales

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Improvements in pharmaceutical research and development (R&D) depend on product innovation. But the number of new compounds approved annually by the U.S. Food and Drug Administration (FDA) has fallen from an average of 35 in 1996–2001 to 20 in 2002–07 (1). This decline stems from several factors (2); however, one particular U.S. regulation—the Paragraph IV patent challenge—is increasingly stifling new drug innovation and deserves our attention.

Paragraph IV Patent Challenges

Although the U.S. patent system has been criticized, particularly when it interferes with access to medications (3), patents are widely used, and there is little debate that they are important for spurring drug innovation (4). In a market system of pharmaceutical innovation, industry revenues support continued R&D, and patents support revenues. The estimated average R&D cost of a new drug brought to market in 2000 exceeded \$800 million (5). Because drug companies are making substantial investments with no certainty about outcomes, they rely on patent-protected revenues to recoup their R&D expenditures (6). Although drugs newly approved by the FDA are awarded 5 years of “data exclusivity” during which generic versions may not be marketed (7), effective patents can offer longer protection by blocking substitute products beyond the 5-year data exclusivity period.

Nevertheless, companies that produce generic drugs can challenge such patents, beginning the process of competing with brand-name drugs after only 4 years (7). To market a generic version, the law requires a company to file an Abbreviated New Drug Application (ANDA) with the FDA that specifies how the generic version relates to the brand-name drug and its patents (7). Paragraph IV permits generic-producing companies to “challenge” each patent associated with the brand-name drug, stating either that

(i) the patent is invalid or (ii) the ANDA does not infringe the patent (7). Although ANDA approvals involving patent challenges generally take from 2 to 3 years (8), the first Paragraph IV applicant is offered 180 days, should their challenge succeed, during which no other generic-producing company may enter the market (7). This incentive to challenge patents allows the successful challenger, without fear of cheaper generics competition, to reap large dividends by pricing just below the brand-name drug (9), earning on average \$60 million per drug (10).

Congress’s Intended Balance

The ANDA and Paragraph IV challenge are elements of the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417, also known as the “Hatch-Waxman Act”). Congress originally intended to strike a balance between two conflicting, but related, policy objectives: ensuring timely, affordable access to drugs, by allowing for expedited FDA approval of generic drugs, and encouraging drug innovation, by restoring some years of patent protection that are lost by firms during the average 1 to 2 years spent in the FDA approval process (8, 11). But the balance is tipping away from the incentives needed to support innovation (12, 13). The Congressional Budget Office estimated that increased competition from generic drugs resulted in a 12% loss in revenues on sales of brand-name drugs (14). This loss exceeded companies’ gains from the patent extensions awarded to them (11).

Sapping Innovation Incentives

These challenges diminish industry revenues and profits, contributing to the current crisis in industry R&D pipelines (15). Because the costs of challenging a patent are a relatively small \$5 million (16) compared with the large average potential payoff of \$60 million in the first 180 days alone (10), generic-producing firms have begun to engage in “prospecting” by filing numerous ANDAs with Paragraph IV challenges. Simple arithmetic suggests that generic-manufacturing companies only need to win a fraction of these to make a prospecting strategy successful. And they are successful: The Federal Trade Commission showed that 72% of Paragraph IV challenges

Development of new but costly pharmaceuticals is put at risk by U.S. law that emboldens generics competition.

PARAGRAPH IV CHALLENGES

Year	Suits filed	Branded drugs involved
2001	35	16
2002	33	16
2003	96	38
2004	90	21
2005	81	33
2006	87	32
2007	162	44
2008	165	43

Paragraph IV Challenges. Since 2001, companies have filed 749 lawsuits responding to Paragraph IV challenges on 243 unique brand-name products (20).

filed from 1992 to 2000 resulted in litigation, with the generic drug challenger winning 42% (8). Moreover, shifts in judicial interpretation of patent laws over the last 3 years have made these challenges easier to launch and win (17).

Paragraph IV challenge suits have been increasing and nearly doubled from 2006 to 2007 (see table, above). Although the upward trend can be traced to legal and regulatory changes made during the last decade (18), the spike in 2007 resulted from a combination of more drugs losing data exclusivity (19) and additional generic-producing companies filing challenges (20). Moreover, the drugs being challenged increasingly have revenues below \$100 million, which shows that “blockbusters” are no longer the only target (19).

Both the type and timing of new products offered to the public are affected. Pharmaceutical companies targeted with Paragraph IV challenges are responding by introducing new products to bolster their at-risk revenues, but these “countering” drugs are more than 90% more likely to be a reformulation or a “next-generation” product, at best marginal improvements over present-day pharmaceuticals, as compared with all other product introductions (12). So, although these new products reach the public sooner, they are much less likely to offer improvement over previous products.

Pharmaceutical firms’ revenues are being severely affected by these challenges. For example, after Merck’s osteoporosis drug

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Fosamax lost a Paragraph IV challenge, Teva Pharmaceuticals began selling its generic alendronate in February 2008, ~4 years before the Fosamax patents were due to expire (21). Fosamax sales subsequently plunged from \$3 billion in 2007 to \$1.5 billion in 2008 (22). Industry-wide, Teva's portfolio of 160 pending ANDAs in 2007 included 92 Paragraph IV challenges, putting at risk over \$100 billion in sales (23).

These challenges are occurring earlier in the life-cycle of brand-name drugs (11, 19), especially for "blockbusters" (24, 25), and successful challenges shorten patent life (19). Thus, without policy intervention, the effective life of key patents will continue to decline, which further compresses the pay-back period during which brand-name firms can recoup R&D investments. The Fosamax case illustrates the dilemma: Although a cheaper version was available to consumers sooner, Merck's revenue loss is roughly equivalent to the expense of bringing two new drugs to market, or nearly 10% of all new drugs introduced in the United States in 2008 (5, 26). Society ought to be concerned about less pharmaceutical innovation, because research shows it is positively related to life expectancy (27) and to lower nondrug medical spending of all types (28).

Evaluation and Prescription

Although the Hatch-Waxman Act was enacted 25 years ago with laudable intentions, lawmakers should now consider altering the length of data exclusivity awards, as research shows that the 5-year allowance is generally insufficient to recoup R&D costs (11, 29). The U.S. National Academies recommends at least doubling the duration

of data exclusivity (29), bringing the U.S. closer to allowances awarded in the European Union, Japan, and Canada (see table, below). Critically, Congress is now debating this issue with respect to biologic drugs: A rule allowing 12-year data exclusivity was reported out of committee (ready to be placed on the legislative calendar) in August despite the White House's support for 7 years (30).

Exclusivity could be extended for "first-in-class" and high-risk, high-necessity drugs, such as preventive medicine for Alzheimer's disease or osteoarthritis (31). Preliminary investigations could allow regulators to create test cases with increased incentives for a subset of drugs across therapeutic categories. Policy-makers could use incentives to encourage private investments in research to complement public research (such as at the NIH) or to offer increased exclusivity to curative and preventive, as compared with palliative, drugs. Auctions could allow companies to bid on specific research projects in return for extended data or market exclusivity. But programs' complexity and administrative burdens should not outweigh benefits.

A robust system of market innovation is built on financial incentives (32). Economic research shows that there is a market failure, and it requires innovative solutions. At a minimum, we should all note that Paragraph IV challenges are contributing to this failure when discussing the future of health care and long-term access to new treatments.

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CHANGES IN NATIONAL DATA EXCLUSIVITY PROTECTION

Region	Data exclusivity regime (years)		Total sales (millions of \$)	Total R&D (millions of \$)
	Former	Present		
European Union	6 to 10	10 + 1	43,661	8,170
Canada	5	8 + ½	6,693	612
Japan	6	8 + 2	9,089	954
United States	5	5	185,209	36,608

Changes in national data exclusivity protection, along with corresponding pharmaceutical sales and R&D expenditures (33–36). The 6- to 10-year range was the result of differences between the national regulatory regimes of E.U. members. These differences in national regimes are the motivation behind the E.U. harmonization to the present 10 years. The +1, +½, and +2 are extensions beyond the base periods that are available to applicants. For example, the +1 in the European Union is available to applicants if they pursue another treatment or therapeutic category for an already approved drug. Sales in the European Union, Canada, and Japan are by United States–owned firms and U.S. divisions of foreign-owned firms. U.S. sales include both United States–owned and foreign-owned firms' sales in the United States. These figures demonstrate the relative size of the relevant markets in which U.S. firms compete. R&D figures reflect investments only by major industrial pharmaceutical companies (e.g., not smaller start-up firms or the government).

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