

Closing the FDA's Orange Book

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THE MISSION OF THE U.S. FOOD AND Drug Administration (FDA) is “to promote and protect the public health by helping safe and effective products reach the market in a timely way.” Unfortunately, that mission has been subverted by a loophole in the Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act, a piece of legislation that was intended to promote generic competition while providing financial rewards for innovative firms that develop new drugs.

Under the act, firms are to list their patents in the FDA's Orange Book. Generic firms, when introducing a competing product, must certify to the FDA that the generic drug would not infringe a patent listed in the book. In the case of a dispute over whether infringement would occur, the FDA allows the courts to decide the matter.

Unfortunately, originator firms are abusing the process to extend their monopoly on certain drugs. The FDA unwittingly abets that abuse by allowing the firms to list new patents in the Orange Book for previously introduced drugs, and by extending automatic protection to the original drug even if the listed patents are invalid or irrelevant.

THE ORANGE BOOK

Generic drugs are typically priced 20 percent to 80 percent lower than the original drug's price. Hence, generics create significant savings for private, corporate, and public consumers. In the United States, the savings from generic prescription drugs are estimated to be over \$10 billion a year.

Since the enactment of the Hatch-Waxman Act, generics' share of prescription drug volume has increased by almost 150 percent. The relaxation of entry barriers under the act has resulted in a significant increase in entry and price competition in drug markets. Today, almost all of the top-selling drugs with expired patents have generic versions

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available, compared to only 36 percent in 1983.

In markets in which the branded drug's patent has expired recently, generic copies quickly gain a large share of the market. A 1998 Congressional Budget Office study of 21 innovator drugs whose first generic competitors entered the market between 1991 and 1993 found that, during the first full calendar year in which those 21 drugs faced competition, generic products accounted for an average of 44 percent of the drugs' prescriptions dispensed through pharmacies. In addition, the Federal Trade Commission has argued that the sooner companies offer the same generic product, the greater the price competition and the lower the price that consumers pay for a generic version of a drug product.

Delaying entry Under the Hatch-Waxman Act, generics were supposed to enter drug markets when the original drug lost its patent protection of 20 years. However, the originator firms have fought to keep generics out of their markets because of the profit losses that occur when generics enter. The originator firms have aggressively used the administrative regulations to their advantage.

To enter the market, a new generic drug must satisfy two requirements:

- It is bio-equivalent to the innovator drug.
- It will not infringe any patents listed in the Orange Book.

Under federal regulations, originator drug companies are supposed to file certain patent information for approved drugs with the FDA. Only patents concerning ingredients, composition, formulation, and method of use are to be filed, and those patents are then listed. Because the FDA is unable to evaluate the relevance of every patent, it relies on originator firms to identify patented drugs for which “infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.”

The FDA has outlined a procedure for determining whether a generic product violates any patents. The generic firm, when filing an “Abbreviated New Drug Application”



AT WHAT PRICE?

A pharmacist prepares a prescription.

(ANDA), must certify to the agency that the generic drug would not violate any applicable patent, or that the applicable patent is soon to expire. The generic firm can also claim that, though the Orange Book lists an unexpired patent for a competing drug, the patent is either invalid or will not be infringed by the generic. That claim, known as a "Paragraph IV certification," is the most common patent status claim made to the FDA.

Advantageous information When a generic firm files a Paragraph IV certification, it must also notify the innovator firm of its application. As part of that notification, the generic firm must provide a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid, is unenforceable, or will not be infringed. That process is advantageous to the originator company because it obtains valuable information about the arrival of competition.

For example, an originator firm might have an active patent for the tablet coating of a brand-name drug, but all other patents for that drug have expired. A generic firm, wishing to compete with the originator, could formulate its own version of the drug that would not have the tablet coating, thus "inventing around" the patent. The generic maker would then file the appropriate paperwork with the FDA, including a Paragraph IV certification. By law, the originator firm would then have 45 days to file a lawsuit claiming the generic offering will infringe on its patent. If a lawsuit is filed, the FDA's approval of the generic drug automatically is stayed for 30 months, regardless of the merits of the case.

If the generic is found to be infringing, the FDA will not approve it until the relevant patents have expired. If, on the other hand, the courts find no infringement or an invalid patent, the FDA will approve the generic immediately. But, because lawsuits typically take more than two years to resolve, the innovator firm is in a position to extend its monopoly by more than two years through simple legal maneuvering.

The law does allow the FDA the option of approving a generic drug if the lawsuit remains unsettled after the 30-month stay expires. However, if the court subsequently finds against the generic firm, the firm is at risk for damages. What is more, if the originator firm lists another patent in the Orange Book during the 30 months' stay, then it is entitled to file a new infringement lawsuit, automatically instituting a new 30-month stay and further extending its monopoly.

HOW OTHER PATENTS WORK

How would a conflicting patent claim normally be treated in another industry? If the good were not a drug and a generic firm wanted to imitate it, the patent laws are much more pro-competitive than the FDA regulations.

Normally, a firm that believes its patent is being infringed will apply to the courts for a preliminary injunction and damages. Until an injunction is granted — and it may not be, depending on the merits of the case — the potentially infringing firm may sell the product. (One of the qualifications required to obtain a preliminary injunction

is that the injunction be in the public interest, a test that is totally absent in the FDA's rule-based approach.)

If a court determines that the product infringes, then the court will award damages. The level of damages is subject to considerable variability depending on a variety of factors; however, courts typically attempt to calculate damages by imagining what the adverse parties would have agreed to had they willingly negotiated a license from the start. Courts also have the discretion to impose triple damages in cases of intentional infringement. That standard permits a wide range of outcomes, which makes infringement a risky proposition. Firms will be willing to enter into a market only if they believe that their product does not infringe, or the patent is in fact invalid. That leads to a more "efficient" level of entry because imitator firms must trade off the potential costs and benefits of entry.

Protection The standard treatment of patents is less protective of the status quo than the FDA regulation of pharmaceutical patents. Originator drug companies receive a preliminary injunction lasting 31.5 months (45 days for the innovator firm to respond, and another 30 months of FDA injunction) regardless of the merits of the case.

That protection of innovator companies apparently was the intent of Congress in the Hatch-Waxman Act. The 30-month period was intended to correspond to the expected average duration of patent infringement litigation, and thus to provide protection to innovator companies during that time. That intention has led to abuse by originator firms because the FDA will not dispute the merits of any of the patents listed in the Orange Book, no matter how weak the originator firms' claims may seem. As Senators Ted Kennedy (D-Mass.) and Orrin Hatch (R-Utah) and Rep. Henry Waxman (D-Calif.) wrote in a letter last summer to Tommy Thompson, the Secretary of Health and Human Services, a "mechanical reading of the law" by the FDA could permit "gamesmanship to undermine competitive interests by allowing late-issued patents to be listed in the [Orange Book] on the eve of generic competition."

Thus, if a generic firm believes that its product does not infringe patents listed in the Orange Book, it cannot simply enter the market. Instead, it will enter the courts. Given FDA regulations, if the originator firm claims infringement, it may be able to maintain its monopoly for an extra year or two, or even longer, until a court decides the merits of the case.

FDA protection of patents would be less of a problem if the agency were merely fulfilling an administrative role of protecting patents registered in the Orange Book at the time the drug was first listed. However, many of the listed patents only specify a new feature or function of the drug that was not patented at the time the drug was first approved by the FDA. Such new patents should not inhibit the genericization of the drug, provided the generic does not infringe the new patents.

THE COST OF DELAY

How large is the potential loss from Orange Book abuse by originating firms? Suppose that, for each patented drug, the

extra protection extends the monopoly by one year. It is estimated that between 2000 and 2005, a number of drugs with total annual sales of approximately \$100 billion will lose patent protection. Considering only a one-year delay in entry and assuming that the generics would get 50 percent of the market share and would price at 75 percent of the originals' (both reasonable assumptions), the delay will cost consumers over \$2 billion annually. What is more, because the generic drug price continues to fall for several years after it is introduced, \$2 billion represents a considerable underestimate of the cost of delaying generic entry by one year.

Case studies There is more than just theoretical evidence for the cost of lawsuit abuse. Consider the following two case studies of how originator firms have used the Orange Book patent-listing process to delay (or attempt to delay) the entry of generics.

Paxil Paroxetine Hydrochloride, introduced to the market under the brand name Paxil, is a mild anti-depressant drug similar to Prozac and Zoloft, though with different indications and a different chemical structure. SmithKline Beecham (now merged with Glaxo) filed for a patent on the basic drug—"paroxetine hydrochloride hemi-hydrate"—as an anti-depressant in 1986. The FDA approved the company's New Drug Application for paroxetine in 1992, and the only patent listed in the Orange Book at that time was the 1986 patent. Paroxetine became widely available soon after that, and had sales of around \$2 billion in 1999.

The fact that paroxetine has been on the market for years has not prevented SmithKline Beecham from claiming further patents for the drug, nor has it stopped the FDA from allowing the company to list those patents in the Orange Book. But a growing number of generic companies are attempting to invent around the patent on paroxetine. In March of 1998, generic manufacturer Apotex filed a Paragraph IV certification claiming a non-infringing version of paroxetine. Three other generic companies filed similar applications by early 2000. In response, SmithKline Beecham has claimed that the generic versions will infringe. Whether the generic firms' applications do in fact infringe on Paxil's patents is now a matter to be determined by the courts.

SmithKline Beecham's other response to the threat of earlier-than-expected generic entry has been a flurry of new patents for which it has obtained listings in the Orange Book. One, in 1998, was for a mix of paroxetine with a liquid so that it could be taken as an oral liquid; three other patents, granted in 1999 and 2000, were for an "anhydrous" (instead of "hemi-hydrate") version of paroxetine hydrochloride. A fifth was granted in 2000 for other paroxetine derivatives (paroxetine methanosulfate). It is questionable whether the 1999 and 2000 patents actually pertain to ("claim") the drug Paxil that was approved by the FDA, or related forms of paroxetine, which would have to undergo bio-equivalence testing before they could be marketed as Paxil.

The benefit to SmithKline Beecham of what Apotex

has labeled "serial patent submission tactics" is evident. Each additional patent listed in the Orange Book triggers the start of a new 30-month stay and, thus, a delay in the onset of generic competition. Although the 30-month stay on Apotex's initial Paragraph IV certification has expired, Apotex still cannot enter because of the newly listed patents.

BuSpar Buspirone, introduced under the brand name BuSpar in 1986, is manufactured by Bristol-Myers Squibb as a medication to treat patients suffering from generalized anxiety disorder. In 1999, Bristol-Myers Squibb sold more than \$600 million of buspirone. The company's patents on BuSpar, which were set to expire at 11:59 p.m. on November 21, 2000, enabled it to sell buspirone for almost 15 years without any competition.

In September of 1998, generic manufacturer Mylan submitted an ANDA to the FDA for a generic version of buspirone tablets. Mylan's ANDA contained a Paragraph III certification stating that it would not market its generic product until the expiration of BuSpar's patent. The FDA "tentatively approved" Mylan's ANDA, with final approval contingent only on the expiration of Bristol-Myers Squibb's exclusivity on November 22, 2000. Anticipating that expiration, Mylan took the steps necessary to put its buspirone product on the market, even loading its trucks with generic buspirone tablets for shipment beginning at midnight.

Only 12 hours before the exclusivity was to expire, the U.S. Patent and Trademark Office issued a new patent to Bristol-Myers Squibb, which the company immediately delivered to the FDA for listing in the Orange Book. Bristol-Myers Squibb also submitted a declaration to the FDA stating that the new patent "is a method-of-use patent covering, among other things, a method of using BuSpar for all of its approved indications." Based on the firm's declaration, and consistent with the FDA's policy of accepting at face value the accuracy of such patent declarations, the FDA listed the new patent in the Orange Book.

Mylan was informed that its ANDA was now incomplete, because it needed to certify that its generic buspirone would not infringe upon the new patent. Mylan's generic buspirone remained on the shipping dock while it—and several other generic firms—contested the validity of the listing. Last March, Mylan was granted a preliminary injunction requiring the FDA to remove the offending patent from the Orange Book on the basis that the patent did not, in fact, appear to "claim" the FDA approved medication. Moreover, 29 states and Puerto Rico recently announced their filing of a lawsuit against Bristol-Myers Squibb over the monopolization. But the net result was that generic competition was held up by about four months simply because the FDA's rules encourage firms to declare that patents "claim" the approved medication in order to extend their monopolies.

CONCLUSION

In response to Orange Book abuse, some policy analysts would have the FDA monitor patents to make sure that

they would support a claim of infringement. But that approach is unlikely to be successful because it is up to the courts to decide whether a particular generic is infringing. Thus, the FDA has correctly decided not to attempt to monitor the listings. But, because the FDA does not judge Orange Book listings, it sustains monopolies that cost consumers billions of dollars annually.

A minimal reform would be for the FDA to not require generic firms to certify to new patents listed in the Orange Book after they have already submitted a substantially complete ANDA application. That would eliminate the most egregious abuses of the regulations. Generic firms would know exactly which patents must be addressed in their application to the FDA. Such a change would require no amendment to the Hatch-Waxman Act or to FDA regulations that are already in place.

A better solution would be for the FDA to withdraw altogether from the business of protecting patents and to concentrate on fulfilling its mandate of ensuring the safety and efficacy of the drugs it approves. Last May, U.S. senators John McCain (R-Ariz.) and Charles Schumer (D-N.Y.) introduced legislation (S.812) that would require originator firms to defend their patents through the courts, applying for injunctive relief when they wished to allege patent infringement. In effect, the McCain-Schumer bill would reduce the 30-month automatic injunction provided by the Orange Book process to 45 days. Those 45 days would allow just enough time for innovator firms to apply for a preliminary injunction against sales by the generic firm. R

READINGS

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