Pharmaceutical Patent Life Extension Strategies: Are REMS Programs Next?

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The Federal Trade Commission (FTC) continues its assault on efforts by branded pharmaceutical companies to get the most out of patents covering their drugs. Undeterred by unfavorable court decisions, the agency continues to pursue “reverse payment” settlements—disparagingly referred to as “pay-for-delay” settlements—of patent infringement litigation with makers of generic drugs. Most recently, the FTC has focused on provisions in which the branded company promises not to launch its own “authorized” generic when the defendant’s generic drug comes on the market on the agreed-upon date. Concurrently, the agency continues to press for legislation that would ban such settlements altogether.

Other practices by branded companies purportedly aimed at forestalling generic entry have invited scrutiny in the past. These include “product hopping,” which involves switching demand to a new, slightly modified product for which the generic product is not substitutable; filing of new patents while the generic company’s application is pending; submitting citizen petitions to the Food and Drug Administration (FDA) during the approval process raising safety issues with the proposed generic; and entering into “pay-for-delay” settlements with generic applicants.

Most recently, attention has focused on practices related to Risk Evaluation and Mitigation Strategies (REMS)—FDA-mandated programs that restrict distribution of drugs that pose safety concerns. The 2007 FDA Amendments Act (FDAAA) (which amended the Federal Food, Drug, and Cosmetic Act (FDCA)) authorized the FDA to require a manufacturer to create a REMS program when its drug is toxic or poses some other safety risk. A REMS program can include restrictions on systems for distributing, procuring, and dispensing the drug. While the FDCA now explicitly prohibits a manufacturer of an approved drug from using elements of a REMS program to block or delay approval of a generic version, some companies have been accused of doing just that.

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Past Challenges to Patent Life Extension Strategies

Several challenges have been mounted over the years to branded companies’ conduct when confronted with the prospect of generic competition. These have been met with varying degrees of success.

“Product Hopping.” “Product hopping,” which involves shifting demand to a modified form of the existing branded drug, is one response. Promoting a “new and improved” version is standard practice in other markets, and is indisputably a feature of healthy competition. But in the generic drug context, switching demand in some circumstances can raise antitrust concerns. Some background is in order.

To market a new drug, a pharmaceutical company must file a New Drug Application (NDA). Preparing an NDA is a laborious and costly process. The company is required to conduct clinical studies of the drug’s safety and efficacy and detail them in the NDA. It must also identify all patents that cover the drug. If the FDA approves the NDA, the drug, accompanied by its patents, is published in the FDA’s “Orange Book.”

The Hatch-Waxman Act of 1984 seeks to encourage generic competition by allowing generic companies to submit Abbreviated New Drug Applications (ANDAs) to the FDA, rather than NDAs. Under the streamlined ANDA process, generic manufacturers are excused from replicating the extensive and costly clinical trials required for a new drug. Instead, they need only show that their product is bioequivalent to the branded drug.

As part of the ANDA process, a generic company must make one of four certifications with respect to the patents listed in the Orange Book: (1) no such patent information has been submitted to the FDA; (2) the patent has expired; (3) the patent is set to expire on a certain date; or (4) such patent is invalid or will not be infringed by the manufacture, use, or sale of the new generic drug for which the ANDA is submitted. These certifications, commonly referred to as Paragraph IV certifications, often lead to patent infringement suits brought against the generic by the branded company.

If the ANDA is approved, the generic drug is listed as being “AB-rated,” or bioequivalent, to the original, “reference” branded drug. This has significant consequences because under state law, pharmacists are allowed—in some states required—to substitute the generic for a prescription for the branded drug. But a generic would not be substitutable for a new formulation, since it has not been shown to be bioequivalent to the new drug. Thus, if the branded company is successful in switching consumers to the new product, generic competition is effectively forestalled.

Critics of product hopping typically assert that changes to the original product are “trivial,” and that the new product is effectively a “sham” created for the sole purpose of delaying competition. Courts have treated the practice

7 Id. at § 355(j)(2)(A)(vii).

differently depending on the facts. In *Abbott Labs v. Teva Pharmaceuticals USA*, Abbott obtained approval for new formulations while Teva’s ANDA was pending. When Teva submitted ANDAs for the new formulations, Abbott obtained approval for yet new formulations. In each case, Abbott withdrew the old formulations from the market, leaving no reference drug for which Teva’s generic formulations could be substituted.

The withdrawal of the reference drugs proved to be decisive in the ensuing Section 2 case brought by Teva. In briefing on the motion to dismiss, Teva urged the court to weigh the benefits of the design changes against the anticompetitive harm. Abbott, relying on the Second Circuit’s decision in *Berkey Photo, Inc. v. Eastman Kodak Co.*, argued that the determination whether the new product was better than the prior drug should be made by the marketplace, not courts. Under *Berkey Photo*, a monopolist’s introduction of a new product is legal if it does not remove competitors from the market and thereby compel consumers to purchase its own product.

The court agreed with Teva’s test and denied Abbott’s motion to dismiss. The court referenced a footnote in *Berkey Photo*:

> [T]he situation might be completely different if, upon the introduction of the [new] 110 system, Kodak had ceased producing the film in the [earlier] 126 size, thereby compelling camera purchasers to buy a Kodak 110 camera. . . . In such a case the technological desirability of the product change might bear on the question of monopolistic intent.

Deference to the marketplace, the court reasoned, only makes sense where the consumers have a choice between the old and new products. Abbott’s removal of the old formulations deprived consumers of that choice; accordingly, Teva was entitled to prove that Abbott’s new formulation was no better.

A different result was reached in *Walgreen Co. v. AstraZeneca Pharmaceuticals*. There, AstraZeneca engaged in a massive marketing campaign to convert patients to the new drug, but left its older product on the market. In a direct purchaser class action, the court granted AstraZeneca’s motion to dismiss, finding that competition was enhanced, not harmed, by AstraZeneca’s introduction of a new, competing product. Unlike Abbott, AstraZeneca’s decision to keep the older drug on the market left consumers free to choose between the two.

The courts’ focus on consumer choice has been criticized. Detractors point to special features of the pharmaceutical market, in which the choice between drugs is made by physicians, not consumers. Abbott’s removal of its old formulations from the market did not prevent doctors from prescribing Teva’s products; it only prevented pharmacists from substituting them for prescriptions for Abbott drugs. Neither consumers nor physicians were coerced. Nonetheless, the rule that emerges from these cases seems clear: when the old, hopped-from

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10 432 F. Supp. 2d 408 (D. Del. 2006).
11 603 F.2d 263 (2d Cir. 1979), cert. denied, 444 U.S. 1093 (1980).
12 *Id.* at 287.
13 *Id.* at 287 n.39.
product remains on the market, an antitrust challenge will likely fail.

Branded companies have also been accused of filing sham applications for additional patents on drugs whose existing patents are about to expire. A recent example is *AFI-AGC Building Trades Welfare Plan v. Pfizer, Inc.*, in which a putative class of third-party payers claims, among other things, that Pfizer filed fraudulent and duplicative patent applications to delay the approval of generic Lipitor.

**Citizen Petitions.** Branded companies have also been accused of “gaming” the FDA approval process by making “sham” regulatory filings. One example is branded companies’ submissions of citizen petitions expressing safety or scientific concerns about the generic drug on the eve of an ANDA’s approval. Until 2007, the FDA could not approve a drug before responding to a citizen petition. Because the process of investigating and responding to a citizen petition could take several months, an eleventh-hour submission could theoretically cause a significant delay in approval of the generic drug company’s ANDA.

A 2002 report by the FTC found that citizen petitions by branded drug companies had not affected the timing of generic entry. Nonetheless, recognizing the potential for abuse, Congress included a provision in the FDAAA prohibiting the FDA from delaying approval of an ANDA based on a citizen petition, unless it determined that “a delay is necessary to protect the public health.”

Further, in the ANDA context, the FDA is required to resolve a citizen petition in 180 days—a period that may not be extended “for any reason.”

The FDAAA also requires petitioners to verify, under penalty of perjury, that the person submitting the petition has not intentionally delayed its filing. To support that, the filer must certify the date on which the information in the petition was first known. In June 2011, the FDA issued guidance explaining its interpretation of requirements. The Guidance cautions that the language of the certification must mirror exactly the language in the statute. By way of example, the Guidance says that substituting “first became known to me” for “first became known to the party on whose behalf this petition is submitted” will not pass muster. As to when the petitioner learned of the underlying information, the exact date—month, day, year—must be provided. Fuzziness will not suffice.

The FTC has not brought any enforcement action premised on frivolous or untimely citizen petitions. Private plaintiffs, however, have pursued the theory in the courts, which have generally refused to dismiss the claims. In

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15 No. 12-0939 (S.D.N.Y. filed Feb. 6, 2012).
16 Plaintiffs also allege that Pfizer employed other anti-competitive tactics, including filing sham citizen petitions and entering into a “pay-for-delay” settlement with the first ANDA applicant. *Id.*
19 *Id.* § 355(q)(1)(F).
20 *Id.* § 355(q)(1)(H).
22 *Id.* at 10.
23 *Id.*
Roxane Labs., Inc. v. SmithKline Beecham Corp., for example, the Eastern District of Pennsylvania recently held that a generic company had standing to assert a claim based on citizen petitions allegedly filed for the purposes of delaying approval of its ANDA. In *In re DDAVP Direct Purchaser Antitrust Litig.*, the Second Circuit reversed the district court’s dismissal, holding that plaintiffs could plausibly show that the citizen petition was a sham and that it caused a delay in generic competition.

Third-party payers and indirect purchasers continue to pursue claims premised on allegedly disingenuous citizen petitions.

**“Reverse Payment” Settlements.** Much has been written about “reverse payment” settlements of Hatch-Waxman patent litigation. When an ANDA applicant certifies that either the branded company’s patent on the product is invalid or its product does not infringe it, the branded company typically sues the generic. Frequently, these cases are settled, with the parties agreeing to generic entry at some point before the branded patent expires.

In many cases, the settlement includes other terms that provide some benefit to the generic. For example, there may be a “side deal,” in which the branded company purchases a license to an unrelated product. There may be an agreement with respect to co-promotion, co-development, manufacturing, distribution, or supply. The settlement agreement might include a promise by the branded company to refrain from marketing its own “authorized” generic when the generic drug comes on the market. Or, the branded company might simply agree to pay cash to the generic.

The FTC considers all of these features to be some form of compensation to the generic for agreeing to delay entry of its product. It assumes that without these provisions, the parties would have agreed to earlier generic entry. Branded and generic companies alike have argued that because parties often differ as to their likelihood of successfully litigating the case, such terms are sometimes necessary to “bridge the gap” and reach an agreement. But the FTC likes to point out that during the period when the only court of appeals to address the issue had held that a reverse payment settlement was illegal *per se*, there were numerous settlements containing no compensation—providing only for entry for some agreed upon period before patent expiration.

In 2005, however, the Eleventh Circuit held that agreements containing compensation to the generic were not *per se* illegal. In *Schering-Plough Corp. v. FTC*, the court held that the question was whether the agreement was beyond the exclusionary potential of the patent. If the settlement, for example, prohibited the generic from marketing some product in addition to that at issue in the case, it would present antitrust concerns. Short of this, any agreement allowing for generic entry prior to patent expiration would be considered lawful—

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25 585 F.3d 677 (2d Cir. 2009).


28 In *re Cardizem CD Antitrust Litig.*, 332 F.3d 896 (6th Cir. 2003).

29 402 F.3d 1056 (11th Cir. 2005).
Despite the presence of additional terms providing compensation to the generic, the FTC and private plaintiffs so far have not had any luck overturning this precedent. The Second and Federal Circuits have adopted the “scope of the patent” test, and the Supreme Court has declined to take the issue up on certiorari.

Undaunted, the FTC continues to press the issue. In 2007, then Commissioner, now Chairman Leibowitz testified that the FTC was looking to bring a case that would create a split in the circuits. In 2008, the FTC sued Cephalon in the Eastern District of Pennsylvania, challenging four settlement agreements involving a total of 13 side deals. And in 2009, the FTC sued Watson, Par and Solvay in the Central District of California, claiming that co-promotion and supply agreements contained in four settlements were inducements to delay entry. That case was transferred to the Northern District of Georgia, which is governed by the Eleventh Circuit’s Schering decision. The court granted Watson’s motion to dismiss; the decision is on appeal. The Cephalon case is pending.

The FTC has also pushed for a legislative solution. Several bills have been introduced that would make reverse payment settlements presumptively illegal, shifting the burden to defendants to show that the challenged agreements are procompetitive. So far, each has stalled in Congress. Recently, Commissioner Rosch has suggested that the FTC might use its rulemaking authority in the meantime to issue a rule that would “deem pay-for-delay agreements as inherently suspect.” Like the proposed legislation, the rule would shift the burden to the settling parties to justify the agreements.

The proposed shift in burden is designed to address a significant proof problem confronted by those challenging reverse payment settlements. The FTC, in particular, is ill-equipped to prove that a side deal is not worth what the parties claim it is. At trial, it would have to establish that the branded company significantly overpaid for the unrelated product, or even that the side deal was a sham—merely a naked payment for delay in disguise. The FTC tried and failed to do this in the Schering case. Proving that co-promotion and distribution arrangements are overvalued presents similar problems. Putting the burden on defendants to defend the value of the arrangements alleviates this problem to a degree.

**Authorized Generics.** The FTC’s current focus is on terms in settlement agreements prohibiting the branded company from introducing its own competing generic when the settling generic company’s product comes on the market.

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“Authorized” generics are branded products that are relabeled and marketed under a generic name. Under Hatch-Waxman, authorized generics are not subject to the 180-day exclusivity rule. First filing generics, though protected from competition from other generic ANDA filers, may have to compete against authorized generics.

Almost half of the settlements investigated by the FTC contain a provision that precludes the branded company from marketing an authorized generic. In the FTC’s view, such provisions are indisputably a means of compensating the generic for agreeing to a later entry date. The presence of an authorized generic on the market during the first filer’s 180-days of exclusivity cuts the first filer’s revenues in half. Thus, an agreement by the branded company to forego introduction of its own generic is of significant value to the generic. The theory is that in exchange for such a promise, the generic must be agreeing to enter later than it otherwise would.

In August 2011, the FTC released a report analyzing the effects of authorized generics on the market for prescription drugs. The FTC found that approximately 25 percent of settlements filed between 2004 and 2010 contained a promise by the branded company not to introduce an authorized generic. In 2010, the number of such agreements increased dramatically—15 were submitted in that year, up from an average of four per year from 2004 to 2009.

Authorized generics have been the subject of debate. Competition from authorized generics during the 180-day period of exclusivity benefits purchasers in the short term; the FTC study found that they lowered prices by 7-14 percent. Some argue that authorized generics harm consumers in the long term, because they diminish a generic company’s incentive to challenge the branded company’s patent. The study found that the promise of reduced revenues had little effect on the number of Hatch-Waxman patent challenges. Authorized generics, it seems, are a good thing. By extension, promises in settlement agreements not to market an authorized generic are a bad thing.

The FTC denigrates such agreements as merely “an attractive way to structure a pay-for-delay settlement.” Since a branded company is foregoing revenue by consenting not to launch its own generic, there is little doubt—in the FTC’s view—that doing so is intended to compensate the generic for delayed entry. Why else, the FTC reasons, would a branded company agree to do such a thing?

Thus far, the FTC has not brought a case based on an authorized generics provision. But such a challenge might be on the horizon. Almost half of the settlements filed with the FTC described as potentially involving a payment for delay included an authorized generics proscription.

From the FTC’s point of view, litigating such a case might be attractive. There are fewer proof hurdles—it need not demonstrate that a side deal, for example, has little or no stand-alone value, or that a branded company does not need the generic’s help in promoting a drug. A branded company’s promise not to launch its own generic, according to the FTC, constitutes a straightforward agreement not to compete, and thus presents a cleaner, simpler issue with a diminished burden of proof.

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37 Id. at vii.
REMS Restrictions: A New Strategy?

A substantial percentage of new drugs are launched pursuant to a REMS, or restricted distribution program. The FDAAA authorizes the FDA to require a REMS if it determines that such a program is necessary to ensure that a drug’s benefits outweigh its risks. REMS restrictions raise antitrust concerns in a couple of ways.

The first arises from the bioequivalence studies a generic company must conduct to gain approval to market its product. To be substitutable for the branded “Referenced Listed Drug,” the generic must be shown to be bioequivalent. Bioequivalence is usually established through testing that compares the two drugs. To conduct such testing, the generic company must acquire an adequate supply of the branded product.

At least one company has invoked its REMS distribution restrictions to deny a generic company access to its product. Celgene Corporation refused to provide Lannett Company with samples of its branded Thalomid®, a drug associated with serious birth defects when ingested during pregnancy. Distribution of Thalomid® is subject to S.T.E.P.S.®, Celgene’s patented managed delivery program. Lannett sought and obtained FDA’s consent to procure samples of Thalomid®, outside of the S.T.E.P.S.® program, to conduct bioequivalence studies. But Celgene, citing safety concerns, refused to supply them without seeing a significant amount of additional information from Lannett.

This prompted Lannett to file a Sherman Act Section 2 claim. Lannett alleged that Celgene withheld the samples to deny it access to the market for thalidomide. Celgene, citing Trinko, countered in its motion to dismiss that nothing in the antitrust laws compelled it to deal with its competitor.

Dr. Reddy’s Laboratories, Inc., a generic manufacturer, complained about Celgene’s withholding of samples of another product covered by a REMS. Dr. Reddy’s tried to obtain samples of Celgene’s Revlimid®, a more potent form of Thalomid®, to conduct bioequivalence studies. As it had with Lannett, Celgene refused Dr. Reddy’s request, saying it “has no obligation to supply” the product. In a citizen petition to the FDA, Dr. Reddy’s complained that a company could use its REMS program to “tie up the supply of a REMS restricted distribution drug product,” and characterized this practice as “nothing more than crude attempts to delay or block generic competition.”

Dr. Reddy’s asserted that such efforts ran afoul of section 505-1(f)(8) of the FDC Act, which prohibits NDA holders from using a REMS program to block or delay approval of a generic.

Celgene filed a citizen petition of its own, objecting to any ANDA for a generic thalidomide product on the ground of safety

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41 See Defendant Celgene Corporation’s Memorandum of Law in Support of Its Renewed Motion to Dismiss, No. 08-cv-3920, at Dkt. 29 (May 28, 2010).
43 Id. at 9.
44 Id.
Addressing an ANDA filed by Barr Laboratories, Inc., the first to seek approval for generic thalidomide, Celgene cited three concerns: (1) the impact of multiple distribution systems; (2) whether Barr’s resources were sufficient for it to create its own distribution system; and (3) issues related to labeling.46

The FDA never resolved Celgene’s or Dr. Reddy’s citizen petitions. Barr withdrew its ANDA for a generic version of Thalomid®, citing the product’s lack of commercial viability.47 In April 2011, the court in the Lannett case issued an order, without opinion, denying Celgene’s motion to dismiss; but in December, the parties settled. No resolution of the issue appears likely in the near future.

Celgene’s refusal to supply samples did, however, trigger an FTC investigation. Celgene’s fourth quarter 2009 SEC filing revealed that the FTC had issued Celgene a CID requesting “information relating to requests by generic companies to purchase our patented Revlimid® and Thalomid® brand drugs in order to evaluate whether there is reason to believe that we have engaged in unfair methods of competition.”48 Referencing the REMS issue, Chairman Leibowitz had warned earlier that “[y]ou can’t let drug safety be used as a tool to delay generic competition.”49 The status of the FTC’s investigation of Celgene is unknown.

Another potential roadblock to generic entry posed by a REMS program is its patentability. In addition to the distribution-related elements to assure safe use, a REMS program often includes a communication plan, a package insert, and sometimes a unique, computerized implementation system. To qualify as a patentable process, a REMS program must be new, useful, and non-obvious.50 The only potential hurdle is non-obviousness: the REMS must be more than a simple variation on established methods of delivering pharmaceuticals.

Theoretically, a patented REMS program can significantly extend the lifespan of the branded product. The branded NDA-holder can list REMS-related patents in the FDA’s “Orange Book.” Generic applicants seeking entry prior to the expiration of all of the branded drug’s listed patents must certify under Paragraph IV that each one is either invalid or not infringed. For major drugs, this invariably results in a patent infringement lawsuit that in turn triggers a 30-month stay in approval.

Celgene’s S.T.E.P.S.® distribution program is patented. In its citizen petition, Celgene describes S.T.E.P.S.® as a “proprietary” system consisting of “a complex network of Oracle database, fax, image storage, telecommunications, and Interactive Voice Response servers.”51 The patent lists a number of specific tests to determine the risk of

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46 Id. at 2.
48 See Form 10-Q Quarterly Report for Celgene Corp. (filed Nov. 2, 2011).
dispensing Thalomid.® Celgene’s citizen petition argues that to obtain approval to market a generic, Barr must implement an equivalent REMS. Celgene warned, however, that “FDA may not rely on the non-public information contained in the Thalomid® application regarding S.T.E.P.S.® to help a generic applicant create its own program.” Moreover, even if Barr were able to create and implement a (non-infringing) equivalent REMS, the existence of multiple distribution systems posed additional safety risks.

Patenting a REMS and listing it in the Orange Book thus can create obstacles for generic manufacturers in addition to the difficulty in acquiring samples. Notably, a REMS patent can be listed and reflected in the labeling for a new drug even when it is not required by FDA.

Yet another hurdle is the labor-intensiveness of a REMS program. According to Celgene, 175 employees are required to implement its S.T.E.P.S. program. Duplicating a comparably complex REMS could be cost-prohibitive for all but the largest generic companies.

**Conclusion**

In the FDAAA, Congress recognized that FDA-mandated REMS programs could be used to thwart generic entry. But according to some, branded companies are nonetheless invoking them to frustrate generic companies from gaining FDA approval. Branded companies’ denial of samples needed to conduct bioequivalence studies has been the subject of at least one Section 2 case and an investigation by the FTC.

Challenging other REMS-related maneuvers, however, could be tougher. A manufacturer seeking approval for a generic product covered by a REMS may have to show both that its own program is equally effective but also that it does not infringe on the branded company’s REMS. Of course, this assumes that the generic company can afford to institute a REMS at all. It remains to be seen whether REMS programs will face antitrust challenges on these grounds.

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54 Id. at 20 n.38.
55 Id. at 18.
56 Id. at 20.