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Analysis&Perspective

Generic Drug Approvals After *Mova:* Is There Any Logic to FDA's Actions?

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The Food and Drug Administration's recent decision to approve an abbreviated new drug application (ANDA) from Kremers Urban Development Co. (KUDCo) for two strengths of generic omeprazole, a drug marketed by AstraZeneca Pharmaceuticals LP under the brand name Prilosec®[1], illustrates the confused state of so-called blockbuster generic drug approvals. As is increasingly the case with such approvals, FDA's omeprazole decision was anything but clear.

Prilosec, an ulcer treatment, has a worldwide market approaching $6 billion and U.S. revenues of approximately $3.7 billion.[2] Thus, FDA's generic approval decision on Nov. 1, 2002, potentially was worth billions of dollars to consumers and to the potential generic manufacturers.

But the gradual erosion of FDA's generic drug regulations through litigation has resulted in regulatory chaos. As a result, it is almost impossible to know what position the agency will take in any given situation, making it increasingly difficult for companies to make business decisions based on their regulatory status.

FDA's omeprazole decision illustrates the point.

Omeprazole Background.

Over several years, AstraZeneca had listed numerous patents on its product with FDA, and at least three generic manufacturers had filed Paragraph IV certifications with FDA stating that those patents were invalid or, if the generic products were approved, their manufacture, use, or sale would not infringe those patents. Under the Federal Food, Drug, and Cosmetic Act (FDCA), AstraZeneca had 45 days after receiving notice of those certifications to sue the generic manufacturers and receive a 30-month stay of FDA final approval of the ANDAs at issue.[3] It did so, and, during the 30-month period, FDA tentatively approved several applications (signaling that they met the statute's approval criteria but could not be finally approved due to ongoing patent disputes).

In an unusual twist, in November 2001, FDA released an opinion concerning 180-day exclusivity for generic sponsors of the drug. The opinion addressed whether any of the ANDA applicants would be eligible for the 180-day period of exclusivity, which is granted to certain "first-to-file" generic applicants under the FDCA.[4] FDA's opinion was issued to clarify a vexing issue: Because AstraZeneca had listed with FDA numerous patents claiming Prilosec, and various ANDA sponsors had certified to different patents, two companies (Andrx and Genpharm) were arguably the "first-to-file," but with respect to different patents.

[1] *See* http://www.fda.gov/bbs/topics/NEWS/2002/NEW00848.html.

[2] *See* http://www.firstcoastnews.com/health/articles/2002-11-02/health_drug.asp.

[3] *See* 21 USC 355(j)(5)(B).

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As is increasingly the case with FDA approvals of generic versions of so-called blockbuster drugs, FDA's omeprazole decision was anything but clear.

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After evaluating this situation, FDA concluded that it could be faced with a "standoff." Under that scenario, "Andrx could not be given final approval until Genpharm's exclusivity for certain patents had run; but Genpharm could not be given final approval until Andrx's exclusivity for other patents had run. . . . [and neither] party could market its drug."[5]

As a result, the agency granted both companies "shared" exclusivity, during which time each could go to market—to the exclusion of all other generic applicants. However, something the agency had not considered came to pass: the U.S. District Court for the Southern District of New York held that Andrx and Genpharm would infringe AstraZeneca's patents upon marketing while a third applicant, KUDCo, would not infringe.[6]

So, what was FDA to do? A review of the last decade's judicial and regulatory activity in this area could lead one to believe that KUDCo could go to market immediately.

Mova[7] and its Progeny

In 1998, the U.S. Court of Appeals for the District of Columbia struck down part of FDA's regulation governing the application of 180-days of generic exclusivity. The regulation required that a generic applicant prevail in patent litigation with an innovator before receiving exclusivity as the "first-to-file" (thus, the regulation was known as the "successful defense" requirement).

FDA had justified the "successful defense" regulation as necessary to avoid absurd results in two situations. The agency reasoned that literal application of the statute would result in unintended delay of approving any generic application when the first generic applicant is not sued or when the first applicant loses its patent suit. Each of those events, it believed, would result in a collective failure to trigger either of the statute's requirements for approving later-filed applications – a decision of a court in patent litigation or first commercial marketing of a generic.[8] The Court of Appeals agreed that such situations were egregious, but held that FDA's regulation was not supported by the statute's plain language. Thus, it struck down the "successful defense" regulation and left FDA to regulate "directly from the statute."[9]

But, FDA's success in doing so was decidedly mixed. It prevailed in some cases,[10] but losses in other cases further eroded the regulatory structure governing 180-day exclusivity and generic drug approvals. With respect to the omeprazole approval, two are worthy of attention.

In *Mylan Pharmaceuticals Inc. v. Shalala*,[11] U.S. District Court Judge Richard Roberts held that FDA could not lawfully ignore patent litigation decisions of district courts before deciding that the statute's exclusivity provision had been triggered.

Under the agency's regulations, exclusivity was not triggered until an appellate court ruled in the patent litigation. Otherwise, FDA asserted, the exclusivity period could expire while the parties were litigating before the Federal Circuit—unfairly depriving the first applicant of exclusivity.

In the second case, also involving Mylan,[12] U.S. District Court Judge Ricardo Urbina ruled that FDA had impermissibly interpreted its regulation governing amendments to Paragraph IV certifications. That regulation[13] requires that an applicant that loses its patent litigation amend its Paragraph IV certification to a Paragraph III certification—thereby indicating to FDA that it does not intend to market any approved drug until expiration of the innovator's patent. When FDA concluded that such an amendment by Barr Laboratories Inc.'s to its ANDA for tamoxifen did not affect its position as the "first-to-file" ANDA, the court ruled that the agency's interpretation of its own regulation was arbitrary and capricious. In other words, once a first-filer loses its patent litigation (even at the district court level), it must amend its Paragraph IV certification to a Paragraph III certification and thus lose its ability to receive 180-day exclusivity. FDA did not appeal the court's decision.

The decision demonstrates the confusion rife in FDA's approval of "blockbuster" generic drugs.

Instead, FDA apparently decided to implement this decision through a change in regulatory interpretation. In 1999, the agency proposed a revised version of its 180-day exclusivity regulations that adopted Judge Urbina's rationale.[14] Under the interpretation announced by the proposed rule and, under the holding in *Mylan v. Henney*, the dire consequences that FDA predicted when it defended the "successful defense" rule would not arise—a district court decision in patent litigation would trigger the exclusivity period, making quicker generic competition more likely. And, should the first applicant in line lose its litigation while a later applicant

[4] *See* 21 USC 355(j)(5)(B)(iv). This provision is designed to give generic manufacturers an incentive to design generic drugs around innovators' patents and, thus, speed the arrival of generic drugs to the marketplace. The first generic sponsor to file an ANDA containing a Paragraph IV certification can receive 180-days of exclusivity, which is triggered by "(I) the date the Secretary receives notice from the applicant . . . of the first commercial marketing of the drug . . . or (II) the date of a decision of a court . . . holding the patent which is the subject of the certification to be invalid or not infringed, whichever is earlier." *Id.*

[5] *See* http://www.fda.gov/cder/ogd/shared_exclusivity.htm.

[6] *Astra Aktiebolag v. Andrx Pharms. Inc.*, Civil No. 99-8926 (S.D.N.Y. Oct. 11, 2002).

[7] *Mova Pharmaceutical Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 1998).

[8] *Id.* at 1067.

[9] *See* FDA, Guidance for Industry: 180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the [FDCA], Procedural Guidance 5 (June 1998).

[10] *See, e.g., Purepac Pharm. Co. v. Friedman*, 162 F.3d 1201 (D.C. Cir. 1998); *Apotex Inc. v. Shalala*, 53 F. Supp.2d 454 (D.D.C. 1999).

[11] 81 F. Supp. 2d 30 (D.D.C. 2000).

[12] *Mylan Pharmaceuticals v. Henney*, 94 F. Supp.2d 36 (D.D.C. 2000).

[13] 21 CFR 314.94(a)(12)(viii)

[14] 64 Fed. Reg. 42873 (August 6, 1999).

prevails, "amendment back" to a paragraph III certification would make the first-filer ineligible for exclusivity and allow the later-filer to go directly to market.

The *Omeprazole* Decision

Under this governing law, KUDCo could go directly to market with its approvable and non-infringing version of omeprazole. But that did not occur. A few weeks after the district court patent decision, FDA "announced" a deal between KUDCo and Andrx under which Andrx would "waive" its claim to exclusivity and allow KUDCo to market omeprazole immediately in exchange for a royalty payment to Andrx.[15] On the same day, FDA formally rescinded its proposed regulation that would have changed its interpretation of the "amendment back" regulation.

Had FDA not rescinded its proposed regulation, Andrx and Genpharm may have had nothing (their ANDA amendments to Paragraph III certifications would have resulted in losing the previously announced "shared exclusivity"), KUDCo could go to market, and consumers would have presumably benefited from lower generic drug prices.

What happened? Perhaps Andrx and Genpharm threatened to sue FDA over its proposed "interpretation" of the "amendment back" regulation.[16] And, perhaps KUDCo was unable to go to market (due to low manufacturing capacity) without first entering a deal with a larger generic manufacturer like Andrx or Genpharm.

Regardless, the decision demonstrates the confusion rife in FDA's approval of "blockbuster" generic drugs.[17]

While FDA's regulations have fallen to judicial scrutiny, the generic industry has grown immensely. It now sells billions in drug products each year. Yet, the *New York Times* recently reported that generic drug prices are rising—meaning that the manufacturers are keeping a larger and larger percentage of the profits from generic sales.[18] Given these two changes in the marketplace, strong arguments can be made that 180-day exclusivity is not needed at all.

Until Congress amends the Hatch-Waxman amendments to FDCA (as many now advocate), however, FDA should develop a regulatory scheme that recognizes the marketplace—one in which there are tremendous incentives for generic manufacturers to design around innovator patents and go to market quickly. The courts have shown the agency a way around the pitfalls it first identified when publishing the "successful defense" regulation. Now, the agency simply needs the will to implement those policies.

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[15] *See* http://www.fda.gov/bbs/topics/NEWS/2002/NEW00848.html.

[16] There is precedent for FDA applying to ANDAs regulations that were in place at the time the ANDA at issue was filed. *See Serono Laboratories v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998).

[17] FDA is now grappling with a decision about generic exclusivity after a remand of *Purepac Pharma. v. Thompson*, — F. Supp.2d —, 2002 WL 31840631 (Dec. 16, 2002). This is another example of a regulatory "toss-up."

[18] Milt Freudenheim, "As Patents on Popular Drugs End, Costs For Generic Drugs Show a Surge," *New York Times*, Dec. 27, 2002, p. A1.

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