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Astellas Loses Court Bid To Fend Off Competition

Astellas Pharma U.S. has failed to win a court ruling that might have helped it fend off generic competition for its Prograf immunosuppressant drug.

The drugmaker had filed a citizen petition September 2007 asking the FDA to establish more stringent standards for companies seeking approval of generic versions of Prograf, including additional bioequivalence studies. The FDA rejected the petition, and Astellas sought a temporary restraining order and preliminary injunction in court to prevent the agency from approving a generic Prograf (tacrolimus).

Judge Ricardo Urbina of the U.S. District Court for the District of Columbia issued a one-page order denying the company's request

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Amphastar: Complaint Targets CDER's Woodcock

Amphastar Pharmaceuticals has filed an ethics complaint against CDER Director Janet Woodcock, claiming she should recuse herself from the approval process for generic Lovenox because of an alleged relationship with Momenta Pharmaceuticals, which also seeks approval of the product.

Amphastar filed the complaint in April, company spokesman Dan Dischner told *Generic Line*. Dischner said the HHS Office of Inspector General (OIG) has informed the company that it is investigating the complaint. The FDA and OIG declined to confirm or deny the existence of a complaint or related investigation.

The FDA collaborated last year with Momenta co-founder Ram Sasisekharan to identify the contaminant in heparin, Dischner said. At the time, Woodcock co-authored papers with Sasisekharan in *The*

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Court: Ultram ER Patents Invalid, In Win for Par Pharmaceutical

Par Pharmaceutical has won a court battle over a proposed generic of Ortho-McNeil-Janssen Pharmaceuticals' Ultram extended-release (ER) that may permit it to market its formulation of the painkiller in the U.S.

The company has tentative FDA approval of the 100- and 200-mg strengths of Ultram ER (tramadol HCl) and intends to review its options with respect to its ANDA, Par says in an Aug. 17 statement.

Judge Kent Jordan of the U.S. District Court for the District of Delaware ruled Aug. 14 that the '887 and '430 patents owned by Purdue Pharma Products are invalid as obvious in light of prior art, according to court documents filed recently. Both patents expire May 2014. This prior art reference includes the previously issued '578 patent, according to the documents.

Jordan issued the ruling despite finding Par had infringed claims of Purdue's patents and that Par had failed to prove Purdue had obtained the patents through inequitable conduct, according to court documents.

Biovail Laboratories holds the NDA for the drug, and Ortho-McNeil, a Johnson & Johnson subsidiary, markets it in the U.S. Biovail isn't a party to the decision as its claims were dismissed Nov. 10, 2008. Ortho-McNeil was dismissed from the action in a Dec. 3, 2008, order, according to court documents.

The decision could have an effect on Biovail's revenue. The company recorded Ultram ER revenue of $37.2 million during the first half of the year, the company says in an Aug. 17 statement.

Canadian drugmaker Labopharm sells a daily tramadol product known as Ryzolt, which is marketed in the U.S. by Purdue. Although Ultram ER and potential generic equivalents aren't automatically substitutable for Ryzolt, Labopharm believes that the launch of Par's generic could affect Ryzolt sales, the company says in the statement.

Purdue will decide whether to appeal the court's ruling. Labopharm is in discussions with Purdue to evaluate the next steps in this matter, the company says.

The plaintiffs originally brought the suit, *Purdue Pharma Products L.P., et al. v. Par Pharmaceutical, Inc., et al.*, in May 2007. — Elizabeth Jones

Mylan Plant Inspection Closed Out by FDA

FDA inspectors found no major deficiencies in Mylan's Morgantown, W.Va., facility despite a recent newspaper report claiming data deletion and failure to heed alerts about deviation from specifications.

Mylan conducted an adequate investigation, FDA spokeswoman Crystal Rice told *Generic Line*. The agency's investigation is officially closed, and it plans no additional action, she added. The FDA sent an establishment inspection report to the company Aug. 12.

The July 26 article in the *Pittsburgh Post-Gazette* claimed plant workers routinely overrode computer warnings about possible problems with the drugs they produced and deleted data records (*Generic Line*, Aug. 5).

Mylan says in a July 28 statement that it "proactively and as a courtesy" informed the FDA about the article. Agency inspectors visited the facility and determined the article's accusations were unfounded, according to the statement.

"The FDA noted there was no evidence of any data deletion," Mylan says in the statement. "All data was reviewed and was present and accounted for; the agency agreed that this was a minor Standard Operating Procedures (SOP) deviation that existed, was fully investigated, and all corrective actions were fully implemented by Mylan."

The company did not respond to a request for further comment by press time. — April Hollis

Appeals Court Affirms Invalidity Of Yasmin Patent

A Bayer HealthCare patent covering its Yasmin contraceptive has been found invalid by a three-judge panel that affirmed a lower court ruling in a case Bayer brought against Barr Laboratories.

The U.S. Court of Appeals for the Federal Circuit upheld in a 2–1 vote a 2008 district court ruling in favor of Barr, which wanted to introduce a generic Yasmin (drospirenone/ethinyl estradiol). The decision held that the '531 patent covering Yasmin (drospirenone/ethinyl estradiol) is invalid due to obviousness, according to court documents. The patent is set to expire in August 2020.

Bayer had maintained that its innovation involved drospirenone that could be micronized to increase its bioavailability and wouldn't require an enteric coating to protect the drug from acid in the body's gastrointestinal system.

Bayer researchers were under the impression that pills containing drospirenone required an enteric coating, according to court documents. Scientists later discovered that a micronized drospirenone pill had the same bioavailability as the enteric-coated version. The patent examiner allowed Bayer's patent claims because "prior art suggested that micronizing drospirenone would not work," according to court records.

However, the U.S. District Court for the District of New Jersey Judge Peter Sheridan ruled in March 2008 that the claims were invalid due to obviousness, saying a person of ordinary skill would have seen micronization as a viable option to improve the dissolution of drospirenone (*Generic Line*, March 19, 2008).

Bayer appealed the decision and also concluded supply and licensing agreements with Barr in June 2008 for generic versions of the oral contraceptives Yasmin and Yaz (drospirenone/ethinyl estradiol). Bayer agreed to supply Barr with the generic product. Barr would distribute the product under the name Ocella. The generic had annual U.S. sales of about $170.2 million for the 12 months that ended Dec. 31, 2008, Teva says in an Aug. 5 statement, citing IMS Health sales data.

Appeals Court Judge Pauline Newman dissented from the majority. "I do not share their view that it would have been obvious to do that which was indisputably unobvious to the experienced formulation scientists," Newman writes in court documents. "Colleagues, employing their own expertise, hold that since the scientists working in this field turned out to be mistaken, it would have been obvious that it was not necessary to take steps to prevent acid degradation."

Bayer Schering Pharma, et al. v. Barr Laboratories, Inc. was decided Aug. 5. — Elizabeth Jones

Barr Recalls One Lot Of Generic Adderall

Barr Laboratories is voluntarily recalling one lot of generic immediate-release (IR) Adderall because some tablets may exceed weight specifications, which may lead to a more potent dose.

No reports have been received of adverse events related to the lot, Teva spokeswoman Denise Bradley told *Generic Line*. Teva bought Barr last year.

Exposure to out-of-specification tablets might cause adverse events such as hypertension, insomnia, agitation and blurred vision, the FDA says in an Aug. 14 emailed statement.

Bradley was not able to provide additional details on the root cause of the problem or corrective actions. The recalled 100-count bottles in lot 311756 were distributed from June 11 to June 16, according to a release posted on the FDA's website.

In 2006, Shire agreed to transfer Adderall IR rights to Barr subsidiary Duramed Pharmaceuticals (*Generic Line*, Oct. 4, 2006). Duramed acquired Shire's Adderall tablets for $63 million after Shire dropped a lawsuit against Barr as part of a patent settlement involving Shire's extended-release Adderall (mixed amphetamine salts). — April Hollis

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New England Journal of Medicine June 5, 2008, and *Nature Biotechnology* April 23, 2008.

Dischner said Momenta had claimed its scientific collaboration with the FDA gave it an edge in seeking the first approval of generic Lovenox (enoxaparin sodium).

Significant revenue is at stake. U.S. sales of Lovenox were about $1.33 billion during the first half of the year, Sanofi-Aventis says in an earnings statement released last month.

Lovenox has been the subject of litigation filed in 2003 by Aventis, which later became part of Sanofi, to stop Amphastar from marketing a generic version. Amphastar filed counterclaims for federal antitrust and unfair competition violations, according to court documents.

However, a federal judge told Amphastar in May that pursuing its counterclaims in the case would be futile without final FDA action on its ANDA for generic Lovenox. The court also dismissed the company's third amended counterclaims, according to court documents.

Amphastar and Teva Pharmaceutical Industries each have filed ANDAs for Lovenox, and Momenta and Sandoz collaborated on an ANDA (*Generic Line*, May 14, 2008).

Pending ANDAs

In 2007, the FDA issued a not-approvable letter to Sandoz and Momenta's ANDA, saying it did not adequately address the potential for immunogenicity of the anticoagulant (*Generic Line*, Nov. 14, 2007). The companies have submitted a proposal to the FDA for addressing the issues.

Momenta did not respond to a request for comment on Amphastar's allegation by press time.

U.S. District Court for the Central District of California Judge Mariana Pfaelzer effectively ended litigation between Sanofi and Amphastar in the case *Aventis Pharma SA, et al. v. Amphastar Pharm Inc, et al.* over the drug in May (*Generic Line*, May 27). — April Hollis

Drug Wholesalers Sue Merck For Generic Singulair Delay

A group of drug wholesalers is suing Merck, saying the company stalled generic competition for its blockbuster allergy drug Singulair.

The plaintiffs, including pharmaceutical wholesalers Louisiana Wholesale Drug and Miami-Luken, accuse Merck of deliberately concealing relevant research when it filed for the '473 patent covering Singulair (montelukast sodium).

The information would have led the patent examiner to reject the claims of the patent, according to the plaintiffs.

Merck subsequently lodged a lawsuit alleging Teva Pharmaceutical Industries had infringed the patent, which has pediatric exclusivity until Aug. 3, 2012, by filing an ANDA for a generic version of the drug, according to court documents.

Generic Competitors

Merck filed the lawsuit "because it knew that the mere filing of such litigation would raise barriers to the entry of generic competition" and delay final FDA approval for Teva's generic version of Singulair, the wholesalers maintain in court documents dated Aug. 11.

The FDA granted tentative approval for Teva's ANDA for the 10-mg version of the product May 21 and for the 4- and 5-mg strengths June 25. The agency could not grant final approval for those applications "because the sham patent infringement litigation remains pending and the 30-month stay under the Hatch-Waxman Act has not yet expired," according to court documents. The stay will remain in effect until November.

Two other generic-drug makers, Roxane Laboratories and Mylan Laboratories, have filed applications to market generic versions of Singulair, but they have been blocked by Merck's anticompetitive conduct, the plaintiffs maintain.

The plaintiffs are seeking treble damages, pre- and post-judgment interest and attorney's fees.

Merck spokesman Ron Rogers told *Generic Line* that the company is aware of the lawsuit but hasn't been served with it. He added that the patent is valid and enforceable.

Singulair had worldwide sales of about $2.32 billion during the first half of the year, according to a Merck earnings statement.

Earlier this year, Article One Partners, a group that looks for evidence that can legitimize or invalidate selected patents, succeeded in its efforts to have the PTO re-evaluate the '473 patent (*Generic Line*, June 10).

Re-Examination

The patent was chosen because it was part of a high-profile case of interest to the group, Cheryl Milone, a spokeswoman for Article One Partners, told *Generic Line*.

As a result of its findings, both Teva and Merck will have additional information on the validity of the patent that can aid them during settlement negotiations, Milone added.

Lawyers representing Merck denied that the PTO's decision is relevant to the case, claiming the office "almost always finds a substantial new question of patentability" in its initial review of re-examination requests, according to a June 1 letter.

"Teva is simply attempting to reargue its case and to inject non-evidentiary information three months after a four-day trial, during which each party presented all relevant evidence including the testimony of its scientific experts," according to the letter.

The suit, *Louisiana Wholesale Drug Co., Inc., et al. v. Merck & Co., Inc., et al.*, was filed Aug. 11 in the U.S. District Court for the District of New Jersey. — Elizabeth Jones

Judge Rebuffs Actavis Attempt To Limit Discovery in Suit

Actavis Totowa has failed to stop plaintiffs in a class action suit from expanding the scope of discovery at its Little Falls, N.J., plant.

The suit is related to the April 2008 Class I nationwide recall of its heart drug Digitek. The litigation was brought after the commercial release of tablets that might have contained twice the approved level of active ingredient, posing a risk of digitalis toxicity in patients with renal failure.

As a result, consumers of the drug filed failure-to-warn suits, which allege that Actavis didn't warn the public of the effects of potentially outsized Digitek tablets in a timely fashion. A number of these suits have been consolidated.

Judge Joseph Goodwin of the U.S. District Court for the Southern District of West Virginia ruled that Magistrate Judge Mary Stanley correctly widened discovery to include Little Falls product batches manufactured before the recall of Digitek (digoxin), according to documents filed Aug. 10.

As a result of this and another recall involving a generic version Ortho-McNeil's Duragesic (fentanyl) transdermal system, the House Energy and Commerce Committee broadened its investigation of alleged FDA shortcomings. The committee more information about Actavis recalls, including the August 2008 withdrawal of all products from a New Jersey plant (*Generic Line*, Oct. 15, 2008).

The plaintiffs had been seeking expanded discovery to include all manufacturing processes at the Little Falls plant for all product lines — a request Actavis opposed. Stanley agreed some further expansion was necessary, but she limited it to records of products whose manufacture immediately preceded the production of the affected lot of Digitek, according to court documents filed July 1.

Actavis challenges the expansion, asserting that Stanley had erred in her decision. The company maintains Stanley had determined Digitek was manufactured uniquely, and it would be "too speculative to expand discovery from one product to another," according to court documents. She permitted discovery of non-Digitek product information — an order at odds with her factual findings, Actavis maintains.

The company also asserts there is no factual evidence to suggest that non-Digitek records might lead to relevant evidence, but there is evidence to the contrary, the company says.

Goodwin ruled that Actavis failed to make its case. The "Magistrate Judge chose a reasonable and prudent means for allowing Plaintiffs access to discovery and, at the same time, turned away the overbroad and expensive fishing expedition they originally proposed," he says in court documents.

Goodwin made his decision in the case, *In Re: Digitek Product Liability Litigation*, Aug. 10. — Elizabeth Jones

Schering-Plough Ends Clarinex Fight With Orchid Over Patents

Schering-Plough has settled a patent lawsuit against Orchid Chemicals & Pharmaceuticals and Orgenus Pharma over their proposed generic versions of solid oral dosage formulations of the allergy drug Clarinex.

The agreement will allow Chennai, India-based Orchid, which had alleged that the ’274 and ’223 patents covering the drug are invalid, to introduce a generic version of Clarinex (desloratadine) orally disintegrating tablets Jan. 1, 2012, and Clarinex 5-mg tablets July 1, 2012, Schering-Plough says in an Aug. 11 statement. Orgenus is a U.S. subsidiary of Orchid.

The agreement is the latest settlement in a series of cases that began in September 2006, when Schering-Plough filed several patent infringement lawsuits in the U.S. District Court for the District of New Jersey against generic companies that wanted U.S. marketing rights for generic versions of Clarinex tablets, Clarinex Reditabs and Clarinex-D12 Hour and Clarinex-D24 Hour (desloratidine/pseudoephedrine sulfate) extended-release tablets. Orchid had alleged the ’274 and ’223 patents were invalid.

All litigation relating to the solid oral dosage form of Clarinex is settled, but litigation is still pending over the drug’s syrup formulation, Fred Malley, a spokesman for Schering-Plough, told *Generic Line*. The company would not comment on the financial details of the settlement.

Schering holds various patents related to Clarinex that extend to 2022. The drug had U.S. sales of $295 million in 2008, the company says.

The cases involving the ’274 patent were consolidated into *In Re: Desloratadine Patent Litigation* in 2007. The dispute over the ’223 patent had been consolidated with *Schering Corporation v. Caraco Pharmaceutical Laboratories, Ltd.* Schering-Plough had accused Caraco of infringing the same patent, but the parties resolved their dispute earlier this year. — David Belian

Drugmakers Launch Generic Imitrex

The FDA has approved nine drugmakers’ ANDAs for generic versions of GlaxoSmith-Kline’s (GSK) migraine treatment Imitrex.

Mylan, Sandoz, Dr. Reddy’s Laboratories, Roxane Laboratories, Cobalt Laboratories, Orchid Healthcare, Aurobindo Pharma and Sun Pharmaceutical Industries all received approval for 25-, 50- and 100-mg sumatriptan succinate tablets Aug. 10.

Ranbaxy Laboratories won approval for its 25- and 50-mg strengths the same day and will launch the product immediately, according to an Aug. 11 statement. The company already markets the 100-mg version of the drug. Ranbaxy had an agreement with GSK that would have allowed it to introduce its generic Imitrex last December. The product launch was delayed when the FDA issued an import alert related to manufacturing violations for two of Ranbaxy’s plants in India, prompting the company to transfer its manufacturing site for generic Imitrex to New Jersey-based Ohm Laboratories, a subsidiary (*Generic Line*, Feb. 4).

FDA spokesman Christopher Kelly told *Generic Line* he was not aware of any updates on the FDA’s review of Ranbaxy’s corrective action operating plan (*Generic Line*, June 10). Ranbaxy spokesman Chuck Caprariello said discussions with the FDA are under way.

Earlier this year, Teva Pharmaceutical Industries announced that it had received final approval for the three dosage strengths (*Generic Line*, Feb. 18). Teva said at the time that it has been awarded the 180-day exclusivity period for the migraine drug because it was one of the first companies to file a Paragraph IV certification.

Imitrex had total U.S. sales of about $934 million for the 25-, 50- and 100-mg strengths during the 12 months ended June 30, Mylan says in a statement. — April Hollis

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Aug. 12. Sandoz announced the next day that it was introducing its generic version of the drug.

The FDA has decided to apply standard bioequivalence testing for approving generic immunosuppressant drugs, including versions of Prograf, Astellas says in an Aug. 12 statement. The company had requested that bioequivalence studies in transplant patients — in addition to those in healthy subjects — should be required for the approval of tacrolimus ANDAs, according to the agency's Aug. 10 response posted on its website.

Astellas contends the agency's current standards for bioequivalence won't ensure the safety of transplant patients who are switched from one immunosuppressant drug to another. The agency also denied Astellas' request for labeling changes that would require that physicians be notified when their transplant patients are about to receive a substitute oral formulation of Prograf.

The agency's decision, "based on inadequate data, to approve a generic version of Prograf, and its failure to impose adequate labeling requirements" would jeopardize patients, Astellas maintains in court documents. The company asked the District Court to issue a declaratory judgment that the FDA acted unlawfully in approving generic versions of tacrolimus. It also wanted the court to compel the agency to require that bioequivalence studies be performed in the transplant patient population, revise Prograf labeling adding warning about substitutions and withdraw approval of any generic version of the drug, according to court documents.

Astellas' citizen petition and lawsuit "represent yet another instance in which a manufacturer of a pioneer drug product in fear of losing its lucrative monopoly has attempted to block generic competition by challenging the scientific basis for FDA's approval of the generic," according to the agency's Aug. 12 motion opposing the preliminary injunction.

The FDA also reiterated its position that its method for approving generic versions of Prograf "uses appropriate bioequivalence standards and is based upon the statute, regulations, and a thorough and rigorous review of the scientific evidence," according to court documents.

"The decision may have a wider impact, potentially with other drugs with a narrow therapeutic index," Chad Landmon, a partner with the law firm Axinn, Veltrop & Harkrider LLP, told *Generic Line*. "This decision shows reluctance at FDA to change its bioequivalence standards for a specific product and to critically evaluate challenges to the standard bioequivalence standards," he added.

Sandoz Approval

Sandoz has introduced the only generic equivalent for Prograf. The drug is part of Novartis' portfolio of immunosuppressants, including Myfortic (mycophenolic acid) delayed-release tablets, indicated for kidney transplants, and Simulect (basiliximab) for the prevention of acute organ rejection, the company says in an Aug. 11 statement.

Prograf is indicated to prevent rejection of transplanted organs in patients receiving allogeneic liver, kidney or heart transplants. The product had annual U.S. sales of about $929 million, Sandoz says in the statement.

Astellas filed its case *Astellas Pharma US, Inc. v. Food and Drug Administration, et al.* Aug. 11.
— Elizabeth Jones

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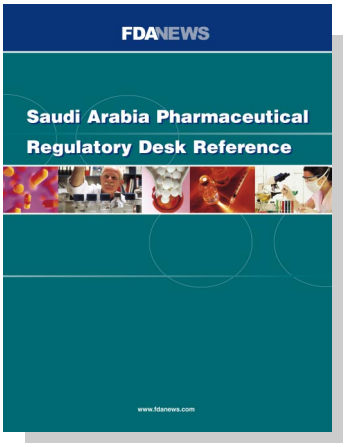

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