Morgan Lewis

PHARMA REVIEW

Dear Readers:

Welcome to the first issue of the Morgan Lewis *Pharma Review*. Each quarter, the *Pharma Review* will summarize key recent cases from the Federal Circuit and district courts that impact the pharma space, including:

- Federal Circuit and district court decisions in Hatch-Waxman litigations
- Federal Circuit reviews of IPR challenges to Orange Book–listed patents
- Appellate and district court decisions in pharma-related antitrust litigations

We hope the *Pharma Review* can serve as a one-stop source for your patent and antitrust pharma-related legal developments.

Happy reading!

PATENTS / OBVIOUSNESS / SECONDARY CONSIDERATIONS

Jeffrey R. Gargano

Earlier Blocking Patent Discounts Evidence of Secondary Considerations

Acorda Therapeutics, Inc. v. Roxane Labs., Inc.
(Fed. Cir. Sept. 10, 2018)

The US Court of Appeals for the Federal Circuit affirmed the district court's finding that Acorda's patents for the use of extended-release formulations of 4-aminopyridine (4-AP) to treat patients suffering from multiple sclerosis (MS) were obvious in view of the prior art. The court discounted the weight of the alleged secondary considerations (e.g., commercial success, failure of others, and long-felt but unmet need) due to an earlier blocking patent. *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 2017-2078, 2017-2134 (Fed. Cir. Sept. 10, 2018) (Taranto, J.).

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In 1997, Acorda licensed a patent from Elan that broadly claimed a method of treating MS by administering a sustained-release formulation containing 4-aminopyridine (4-AP). Shortly thereafter, Acorda began investigating the use of 4-AP to treat MS and conducted studies that resulted in Acorda filing and obtaining its own patents directed to (1) a 10 mg dose of 4-AP administered twice daily; (2) a stable sustained-release formulation of 4-AP; (3) dosing to achieve 15-35 ng/mL serum levels of 4-AP; and (4) improved walking in MS patients. The broader Elan patent and the more specific Acorda patents were Orange Book–listed for Acorda's Ampyra®, a 10 mg 4-AP sustained-release tablets for twice daily administration.

The defendants, Roxane Laboratories, Mylan Pharmaceuticals, and Teva Pharmaceuticals USA, submitted Abbreviated New Drug Applications (ANDAs) seeking approval to market generic versions of Ampyra. In July 2014, Acorda sued the defendants in the Delaware district court alleging infringement of claims in each of the Elan and Acorda patents. At trial, the defendants stipulated to infringement but challenged the validity of the asserted claims. The district court held the asserted claims in the Acorda patents invalid for obviousness, but the court upheld the validity of the asserted Elan patent claims and enjoined the defendants until the Elan patent expired on July 30, 2018.

On appeal, Acorda raised three arguments regarding the district court's obviousness ruling. First, Acorda argued that the district court erred in finding that a person of ordinary skill in the art (POSA) would have had a motivation to combine the prior art to arrive at the Acorda inventions and a reasonable expectation of success in doing so. Second, Acorda challenged the court's determination that the claimed 4-AP serum levels—15-35 ng/mL—are inherent in the claimed dosage (e.g., 10 mg of 4-AP administered twice daily). Third, Acorda argued that the court applied a categorical rule that a blocking patent negates any findings in favor of Acorda on secondary considerations.

Acorda argued that because the prior art disclosed improvement in walking when MS patients were administered 17 mg of 4-AP twice daily, a skilled artisan would not be motivated to modify the dose, with a reasonable expectation of success, to the claimed 10 mg of 4-AP twice daily. The Federal Circuit noted that the prior art (1) did not disclose that dosages lower than 17 mg twice daily would *not* be effective in improving walking in MS patients; and (2) warned that seizures may occur at higher doses. Accordingly, the Federal Circuit concluded that the district court did not err in finding that a POSA would look to lower doses with an expectation of success.

Next, Acorda argued that a skilled artisan would not have a reasonable expectation of success because the prior art did not teach or suggest the 4-AP serum level limitation of the claims (i.e., levels in the 15-35 ng/mL range). The Federal Circuit rejected this argument for three reasons. One, the prior art taught that a twice daily dose of 10 mg sustained-release 4-AP would result in a 4-AP average serum level of 20.8 ± 5.7 ng/mL. Two, counsel for Acorda on oral argument admitted that "it was known in the art that a sustained-release formulation of 10 mg twice daily could achieve that pharmacokinetic result." Three, Acorda did not point to any evidence that another sustained-release formulation containing the same dose of 4-AP but other excipients would produce a different pharmacokinetic profile.

Finally, Acorda contended that the district court erred when it discounted the objective indicia of nonobviousness as it related to the Acorda patents. At trial, Roxane's expert opined that other entities that might want to pursue a commercial opportunity like Ampyra would not have access to the sustained-release 4-AP formulation claimed in the broad Elan patent because Acorda owned the exclusive rights to that formulation. Based on this evidence, the district court concluded that "the risk of infringement liability [for marketing in the United States] would have provided an independent incentive for a patentee not to develop the invention of the Acorda patents, even if those inventions were obvious." The Federal Circuit agreed and found that the district court was correct in discounting any commercial success, failure of others, or long-felt but unmet need due to the Elan blocking patent.

The defendants' cross-appeal of the district court's ruling that the Elan patent was not invalid was dismissed as moot because the Elan patent had expired and no respective liability was at issue.

PATENT VENUE

Kevin Shortsle

Residency of a Nonparty May Be Imputed to Defendant Where Entities Take On an Alter Ego Relationship

Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc. (D. Del. Oct. 18, 2018)

Addressing whether residency of one entity can be imputed to another for purposes of the patent venue statute, the US District Court for the District of Delaware held that residency can be imputed for purposes of satisfying the first prong of 28 U.S.C. § 1400(b), but that Bristol-Myers Squibb Company (BMS) failed to meet the heavy burden of proving an alter ego relationship between defendant Mylan Pharmaceuticals Inc. (MPI) and its wholly owned Delaware subsidiary, Mylan Securitization LLC. Separately, Judge Stark held that patent infringement cases arising under the Hatch-Waxman Act are governed solely and exclusively by Section 1400(b), not Section 1391. *Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc.,* Case Nos. 17-374, -379 (D. Del. Oct. 18, 2018) (Stark, C.J.).

MPI, incorporated in West Virginia, filed a motion to dismiss for improper venue based on the US Supreme Court's *TC Heartland* decision. The court denied MPI's motion without

prejudice, but ordered venue-related discovery. After eight months of discovery, MPI renewed its motion to dismiss for improper venue. MPI argued that it is not incorporated in Delaware, did not perform the alleged act of infringement in Delaware, and does not maintain a regular and established place of business in Delaware. In addition, MPI argued that the residency of a nonparty affiliate, Mylan Securitization, should not be imputed to it based on common law doctrines of "alter ego" and "piercing the corporate veil." Finally, MPI argued that even if these common law doctrines applied, BMS failed to meets its burden of proof.

BMS argued that the Delaware residency of Mylan Securitization should be imputed to MPI due to an alter ego relationship between the two entities. BMS only argued for proper venue under the first prong of Section 1400(b) (i.e., residency), and not the second prong (i.e., acts of infringement and regular and established place of business) because there was insufficient discovery on the second prong. BMS asserted an alter ego relationship based on Mylan Securitization (1) being a wholly owned subsidiary of MPI, (2) having none of its own employees, revenue, profits, or facilities, (3) being represented by the same lawyers in transactions with MPI, (4) having minimal costs of operation, and (5) sharing an overlapping director with MPI. BMS alternatively argued that in the Hatch-Waxman context, venue should be governed by Section 1391, not Section 1400(b), and under Section 1391, there is no dispute that venue was proper in Delaware.

Turning first to the question of whether residency may be imputed under the first prong of Section 1400(b), the court agreed with BMS, holding that piercing the corporate veil and imputing one entity's residence may be appropriate where one entity acts as the alter ego of the other. The next step in the court's analysis focused on overcoming the presumption that corporate entities are legally distinct. Applying Third Circuit law, the court analyzed whether BMS made a showing of fraud, injustice, or unfairness that would allow the court to impute residency.

The court determined that BMS failed to meet its heavy burden and dismissed each of BMS's arguments in turn. The court found that BMS failed to produce any evidence showing corporate formalities were ignored or anything improper or illegal occurred when creating Mylan Securitization. The court found that there was nothing improper about creating a wholly owned LLC for tax purposes; there was no evidence of undercapitalization or insolvency of MPI based on its relationship with Mylan Securitization; and the structure of the MPI and Mylan Securitization was for the legal purpose of increasing the amount of cash to MPI. It also found that using the same lawyers in a transaction was not improper because the transactions were not secret and there was no evidence of a sham or fraudulent negotiation. Finally, the court found no fault in sharing one overlapping director, which did not show that corporate formalities were ignored. Most importantly, the court found that BMS failed to show any evidence of fraud, unfairness, or injustice. Accordingly, the court refused to impute MPI with the residency of Mylan Securitization, and dismissed the case for improper venue.

The court also dispensed with BMS's alternative argument, that Hatch-Waxman patent infringement cases should be governed by Section 1391, not Section 1400(b). The court held that because Hatch-Waxman cases arise out of the patent statute, and the 30-month stay of generic approval is triggered by bringing a patent infringement action, Hatch-Waxman litigation is incontestably an action for patent infringement. Accordingly, the court held that *TC Heartland* governs venue for Hatch-Waxman litigation, which holds that venue is governed solely and exclusively by Section 1400(b).

ANTITRUST / SUFFICIENCY OF PLEADINGS

Shon Lo

Direct Purchasers Failed to Sufficiently Plead *Walker Process* Fraud and Sham Litigation by Novartis

United Food & Commercial Workers Unions & Employers Midwest Health Benefits Fund et al. v. Novartis Pharms. Corp. (1st Cir. 2018)

The US Court of Appeals for the First Circuit affirmed a district court's dismissal of direct purchasers' antitrust lawsuit concerning Novartis's Gleevec™ product under Fed. R. Civ. P. 12(b)(6). The direct purchasers invoked the *Walker Process* fraud and sham litigation exceptions to *Noerr-Pennington* immunity in support of their antitrust claims. *United Food & Commercial Workers Unions & Employers Midwest Health Benefits Fund et al. v. Novartis Pharms. Corp.*, 902 F.3d. 1 (1st Cir. 2018) (Barron, J.).

The *Walker Process* fraud allegations were based on Novartis's actions in obtaining a follow-on patent for the #-crystalline (non-needle) form of imatinib mesylate, the active ingredient of Gleevec. At the time the patent was filed, imatinib and its salt forms were known in the prior art. The examiner rejected the claims as anticipated and obvious, but the Patent Trial and Appeal Board reversed, reasoning that even assuming the mesylate salt was anticipated, the #-crystalline form of the mesylate salt was neither anticipated nor obvious.

The direct purchasers alleged that Novartis fraudulently procured the patent by falsely representing in the specification that the prior art did not disclose imatinib mesylate and that the discovery of its #-crystalline form was "surprising." But both the district court and First Circuit found that these representations, even if false, were not material to the issuance of the patent.

First, Novartis in fact had submitted two prior art references that disclosed imatinib mesylate to the US Patent and

Trademark Office before the patent issued. It did so after the examiner had issued a Notice of Allowance, but the court found the examiner must have considered those references prior to issuance. Thus, the allegedly false representation in the specification did not meet the heightened "but-for" materiality standard to support *Walker Process* fraud. Second, the court found that a bare assertion that an invention is not obvious "is not in and of itself a material misrepresentation for purposes of *Walker Process* fraud." Finally, the court rejected the plaintiffs' arguments that these two alleged misrepresentations rose to the level of an "unmistakably false" affidavit or declaration.

The plaintiffs based their sham litigation claim on allegations that Novartis's infringement lawsuits against ANDA filers were objectively baseless because the only reasonably foreseeable outcome of those lawsuits was dismissal on patent-invalidity grounds. However, the plaintiffs failed to identify a single precedent that permitted an antitrust sham litigation claim to go forward based on an allegation that the infringement litigation was objectively baseless because the underlying patent was alleged to be invalid due to anticipation or obviousness. Without reaching the subjective motivation prong of sham litigation, the court rejected the plaintiffs' contentions, and affirmed dismissal.

PATENTS / OBVIOUSNESS / OBJECTIVE INDICIA

Krista Vink Venegas

Prior Art Failed to Carry the Day and Unexpected Results Supported Validity of Opioid Addiction Treatment Patent

Orexo AB v. Actavis Elizabeth LLC (Fed. Cir. 2018)

The US Court of Appeals for the Federal Circuit reversed the US District Court for the District of Delaware, finding that it erred in invalidating as obvious claims to a combination opioid addiction medication in view of the prior art and substantial evidence of objective indicia of nonobviousness. *Orexo AB v. Actavis Elizabeth LLC,* 903 F.3d 1265 (Fed. Cir. 2018) (Newman, J.).

Orexo's patent titled "Abuse-Resistant Pharmaceutical Composition for the Treatment of Opioid Dependence" is Orange Book–listed for Zubsolv®. Actavis filed an ANDA to market a generic version of the product prior to patent expiry, resulting in this Hatch-Waxman litigation.

The issue on appeal was whether Actavis proved by clear and convincing evidence that the claims to a sublingual buprenorphine/naloxone/citric acid product were obvious where compositions with a 4:1 ratio of these active ingredients were known and where reducing pH with citric acid was known to enhance bioavailability. The court found Actavis had not met its burden because the claimed arrangement of the formulation was not known or suggested and the resulting benefits were unexpected.

Prior to the filing of the Orexo patent, there had been significant research and development of medications for treating opioid dependence, including the use of partial opioid agonists like buprenorphine in sublingual tablets such as Subutex®. It had been discovered that adding the opioid antagonist naloxone in a 4:1 ratio with buprenorphine (such as in Suboxone®) provided both an optimal sublingual treatment (because naloxone has minimal transmucosal absorption) and a reduction in potential abuse by drug users injecting dissolved buprenorphine tablets (because injected naloxone blocks the action of buprenorphine). However, there was a continuing need for safer and more effective opioid dependence therapies.

Orexo's patent disclosed a formulation having a 4:1 ratio of buprenorphine and naloxone, but where the buprenorphine is adhered *on the surface* of microparticles of citric acid/naloxone rather than being in a homogeneous mixture. Using this arrangement, Orexo found buprenorphine is rendered more bioavailable, and therefore lower amounts of each active ingredient can be used in each tablet. During the litigation, there was no dispute that this formulation led to more effective treatment due to a 66% improvement in bioavailability with a 29% reduction in buprenorphine.

However, following trial, the district court found the asserted claims invalid because "a skilled artisan would obviously have selected these components from the prior art and reformulated them" as claimed. The court found (1) Orexo's own prior application disclosed "that 'a person of ordinary skill in the art' would have been motivated to reformulate Suboxone tablets . . . to improve bioavailability"; (2) the Suboxone patent disclosed that "the addition of citric acid facilitated an increased level of buprenorphine"; and (3) a European prior art patent disclosed that "the use of citric acid with an interactive mixture would also improve [buprenorphine] bioavailability." The court posited that while the increased bioavailability of the claimed product provided some support for nonobviousness (but only a difference of degree, not kind), Orexo's evidence of long-felt need, copying, and teaching away was irrelevant because the ratio was not expressly claimed.

On review, the court found that the prior art "[did] not show or suggest the claimed combination [or] that the claimed combination would achieve enhanced therapeutic effect while being less subject to abuse." Specifically, the court took issue with the characterization of Orexo's patent and the European patent, which did not teach or suggest using citric acid particles as a *carrier* for buprenorphine and showed mixed results at best as to bioavailability of active ingredients. In fact, at the oral argument, Acavis conceded that "no reference teaches using citric acid as a carrier particle, or that citric acid should be used as a carrier particle," and no reference taught that structure to improve bioavailability.

Further, with respect to objective indicia of nonobviousness, the court found the benefits of the formulation maintaining the 4:1 ratio with naloxone while enhancing bioavailability

by 66% significant and unexpected in view of the examples set forth in the European patent, which included only a general teaching of interactive mixtures.

Therefore, the court found a lack of clear and convincing evidence of a teaching or suggestion to use citric acid as a carrier to enhance efficacy and further diminish the potential to abuse the claimed combination product.

PATENTS / OBVIOUSNESS

Amanda S. Williamson

Federal Circuit Upholds Two Patents Covering Endo's Aveed®

Endo Pharm. Solutions Inc. et al. v. Custopharm Inc. (Fed. Cir. 2018)

The US Court of Appeals for the Federal Circuit upheld claims from two Orange Book–listed patents covering Endo Pharmaceutical Solutions Inc.'s Aveed®, rejecting Custopharm Inc.'s arguments that the asserted claims were invalid for obviousness. *Endo Pharm. Solutions Inc. et al. v. Custopharm Inc.*, 894 F.3d 1374 (Fed. Cir. 2018) (Chen, J.).

Endo holds the approved New Drug Application for Aveed®, and Bayer owns the two Orange Book formulation patents at issue. Aveed® is a long-acting injectable testosterone replacement therapy for men suffering from physiologically low levels of testosterone, also known as hypogonadism. Aveed®'s patented formulation has several advantages over prior therapy: After two initial injections, it is administered less frequently; it works for all men suffering from hypogonadism without personalization by the treating physician; and patients on Aveed® avoid fluctuations in testosterone levels associated with other therapies.

In 2014, Custopharm's predecessor submitted an ANDA seeking FDA approval for a generic version of Aveed®. Endo and Bayer filed suit alleging infringement of two patents covering Aveed®'s novel formulation. The patents-in-suit disclose three primary elements: 750 mg dosage of testosterone undecanoate (TU); 40% castor oil and 60% benzyl benzoate co-solvent vehicle formulation; and a specific two-stage dosage schedule.

During the district court proceedings, Custopharm stipulated to infringement and argued that the asserted claims were invalid as obvious. In support of its obviousness arguments, Custopharm relied upon three articles describing clinical studies involving 1,000 mg TU injections. Custopharm acknowledged that the articles did *not* disclose a 750 mg dosage or the use of a co-solvent vehicle formulation. After holding a bench trial, the district court rejected Custopharm's obviousness arguments and upheld all claims. Custopharm appealed.

On appeal, Custopharm argued that one of skill in the art would have recognized that the patients who were studied in the articles were being overdosed at 1,000 mg of TU and thus would have been motivated to reduce the dosage to 750 mg. Custopharm further argued that such a dose adjustment would have made it obvious to adjust the injection interval to use the claimed two-phase dosing regimen.

The Federal Circuit disagreed. Citing the FDA's commonly accepted TU dosage guidelines, which included a 1,000 mg dosage, the court found that one of skill in the art would not have been motivated to decrease the previously disclosed dosage to 750 mg. The court further relied on statements in one of the articles reporting that a single 1,000 mg injection of TU resulted in prolonged action without higher than normal testosterone levels as evidence that one of skill in the art would not have been motived to lower the 1,000 mg dosage. Accordingly, the Federal Circuit found that the lower court reasonably rejected Custopharm's obviousness arguments based on an overdose theory.

Custopharm also argued that the vehicle formulation (i.e., 40% castor oil and 60% benzyl benzoate co-solvent) was inherently disclosed because the articles provided a "detailed recitation" of the TU composition's pharmacokinetic performance, and it was later disclosed that the same formulation identified in the patents-in-suit was used by the articles' authors. Custopharm argued that a skilled artisan could derive the vehicle formulation based on that disclosed pharmacokinetic performance.

The Federal Circuit again disagreed, finding that Custopharm failed to present clear and convincing evidence that the articles *necessarily* disclosed the vehicle formulation as required for inherency. As the Federal Circuit explained, there were many potential co-solvents in the prior art, and Custopharm failed to demonstrate that the pharmacokinetics could only be achieved using the claimed vehicle formulation of 40% castor oil and 60% benzyl benzoate. Thus, the Federal Circuit found that Custopharm failed to establish that the articles inherently disclosed the claimed vehicle formulation.

CLAIM CONSTRUCTION / PRELIMINARY INJUNCTION

Brittany A. Washington

Federal Circuit Overturns Preliminary Injunction for Suboxone Film

Indivior Inc. v. Dr. Reddy's Labs., S.A. (Fed. Cir. Nov. 20, 2018)

The US Court of Appeals for the Federal Circuit vacated and remanded a lower court ruling and found that the decision to grant the patentee a preliminary injunction was based on an erroneous interpretation of claim scope. *Indivior Inc. v. Dr.*

Reddy's Labs., S.A., Case Nos. 2018-2167, -2169 (Fed. Cir. Nov. 20, 2018) (Stoll, J.) (Newman, J., dissenting).

The case involved a patent directed to Suboxone® Film, a treatment for opioid dependency. The film is generally formed by mixing active ingredients with excipients, casting the mixture on a surface to form a wet film, and controllably drying the film to produce a solid sheet. The patent at issue shared the same specification as a parent application. Indivior asserted the parent patent against Dr. Reddy's in a previous litigation. There, the court held Indivior failed to show Dr. Reddy's infringed the parent patent. Specifically, the court determined that Indivior disavowed producing the claimed films by solely using conventional top air drying. The court, therefore, construed the claim terms "dried" and "drying" to mean "dried without solely employing conventional convection air drying from the top." After the court's finding of noninfringement, Indivior amended the instant claims during prosecution by replacing the terms "dried" and "drying" with the term "continuously cast." Indivior also filed a terminal disclaimer to overcome obviousness-type double patenting rejections based on the parent patent. Upon issuance of the patent, Indivior asserted the revised claims against Dr. Reddy's and moved to enjoin it from selling its generic film product. The lower court granted Indivior's preliminary injunction. Dr. Reddy's appealed.

On appeal, the Federal Circuit found the lower court abused its discretion in granting the preliminary injunction. The court examined the patent specification and determined it was "rife with remarks that disparage, and therefore, disclaim" using solely conventional top air drying to produce the films. Indivior argued the claims were not limited to any particular drying method because the terms "dried" and "drying" were absent from and had no textual basis in the claims. The court disagreed, explaining that (1) the drying limitation had a textual basis in the claim language "continuously cast film," and (2) the specification made clear that the invention did not include films dried using conventional top air drying. The specification warned that conventional top drying methods could not achieve the claimed level of drug content uniformity. Such methods produced a "ripple effect," resulting in "an uneven, and therefore non-uniform film."

Indivior further argued that importing the drying process limitation into the patent's product claims was improper. The court acknowledged that, generally, product claims are not limited to the method of manufacture disclosed in the specification. However, "if the patentee has made clear that the process steps are an essential part of the claimed invention," those steps can be read into the product claim. The court explained that the claim term "continuously cast film" described the film-formation process taught in the specification, which necessarily required performing the drying steps. Therefore, the drying process was an essential part of the claimed invention and was properly read into the claims.

Finally, the Federal Circuit held that claim preclusion likely barred Indivior's suit because the claims of the asserted patent and those of its parent are "patentably indistinct." Although Indivior substituted the terms "dried" and "drying" with "continuously cast" in the asserted claims, the court explained the scope of the claims did not materially change given the disavowals made in the patents' shared specification. The court also found that Indivior's filing of a terminal disclaimer was a "strong clue" that the claims of the two patents were patentably indistinct. Thus, the court held that claim preclusion likely applied.

Judge Newman dissented, arguing that the preliminary injunction was equitable relief granted under the discretion of the district court. Judge Newman disagreed with the district court that the drying limitation could be found in the asserted patent because no such limitation was found in the claims. Moreover, Judge Newman found the majority's reliance on the district court's judgment with respect to the parent patent to support a finding of claim preclusion to be improper—noting that the claims of the asserted patent are different than those in the parent patent and that the judgment with respect to the parent patent was pending appeal.

INFRINGEMENT / DOCTRINE OF EQUIVALENTS

Richard W. Martin

Delayed-Release Claims Infringed Under the Doctrine of Equivalents

Galderma Labs. v. Amneal Pharm., LLC (D. Del. 2018)

In a heavily redacted opinion, the US District Court for the District of Delaware held after a bench trial that Amneal's proposed generic version of Oracea infringed Galderma's patents under the doctrine of equivalents (DOE). Thus, despite formulation changes that avoided the literal scope of the claims, the court nonetheless found Amneal's ANDA product performed the same function, in the same way, to achieve the same result claimed in the asserted Oracea patents. The court also held that the differences between the proposed generic and the claimed composition were insubstantial under the DOE. *Galderma Labs. v. Amneal Pharm., LLC,* Civil Action No. 16-207-LPS, 2018 (D. Del. Aug. 27, 2018) (Stark, J.).

Oracea is an oral rosacea treatment formulated for once daily administration to maintain doxycycline blood concentrations within a specified range. The formulation comprises two types of doxycycline beads within a gelatin capsule: immediate-release beads and delayed-release beads. The asserted claims of Galderma's patents recite formulations and methods with these two doxycycline types, which together provide various pharmacokinetic and pharmacodynamic advantages.

The precise formulation of Amneal's product is redacted, but the opinion indicates that the proposed generic achieves the same doxycycline blood concentrations as Oracea using a once daily dosing regimen, achieves early and sustained release, but does not include a distinct delayed-release doxycycline component.

Before turning to its DOE analysis, the court considered whether Galderma was precluded from asserting infringement under the doctrine. First, the court held that an equivalence finding would not vitiate the "delayed release" claim element because a portion of the doxycycline in the ANDA product was not immediately released (i.e., the ANDA formulation achieved sustained doxycycline release, the very equivalent at issue). Next, the court found that while prosecution history estoppel applied, Galderma adequately rebutted the presumed surrender of claim scope because the narrowing amendments did not relate to patentability of the delayed-release term at issue. Finally, the court found no prosecution disclaimer by Galderma's expert during inter partes review proceedings because his statements did not constitute a "clear and unmistakable" disavowal of claim scope regarding delayed-release formulations.

The court then applied US Supreme Court DOE precedent to find infringement under either insubstantial differences or function-way-result tests. The court held that the ANDA product is insubstantially different from the delayed-release claim element because, looking at the product combination as a whole, it delays release "until a time other than immediately following oral administration." Applying the function-way-result test, the court held that (1) the ANDA product functions to delay release of doxycycline, (2) it does so by way of a delayed-release formulation, and (3) it thereby achieves the same result as the asserted claims.

Galderma did not prevail on all asserted patents. Notably, the court found no DOE infringement of one of the asserted patents that expressly required an enteric polymer coating because, for those claims, Galderma failed to establish that Amneal's product included a component insubstantially different from the coating. The court also held that Galderma was collaterally estopped from asserting infringement of two remaining patents in view of earlier litigation. The court rejected Galderma's argument that an earlier case did not present the identical issue because it had not asserted equivalency in that case, stating that "[d]octrine of equivalents infringement is one theory of infringement, not a distinct issue itself."

The court also considered various invalidity defenses, finding the claims enabled, adequately described, sufficiently definite, and neither anticipated nor obvious in view of asserted prior art references.

PATENTS / OBVIOUSNESS

Caroline S. Lourgos

Delaware Court: Patent Covering Blood-Thinning Drug Xarelto Not Obvious

Bayer Intellectual Prop. GmbH v. Aurobindo Pharma Ltd. (D. Del. July 13, 2018)

After a bench trial, the US District Court for the District of Delaware found a patent covering the chemical compound of rivaroxaban valid because it would not have been obvious to select a specific lead compound or modify that lead compound to develop the active ingredient in Xarelto. *Bayer Intellectual Prop. GmbH v. Aurobindo Pharma Ltd.*, No. CV 15-902 (D. Del. July 13, 2018) (Stengel, C.J., E.D. Pa., sitting by designation).

Bayer and Janssen alleged infringement of the patent covering rivaroxaban, the active ingredient in Xarelto. Xarelto is a Factor Xa inhibitor that is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, treat deep vein thrombosis and pulmonary embolism, and prevent deep vein thrombosis and pulmonary embolism in patients undergoing knee or hip replacement surgery.

The defendants stipulated to infringement and argued that a POSA would have been motivated to choose linezolid as a lead compound for developing a Factor Xa inhibitor and modify that compound to make rivaroxiban with a reasonable expectation of success. Linezolid is an oxazolidinone compound that was in clinical trials for antibiotic indications at the time of the invention.

Under the first prong of the lead-compound analysis, the defendants argued that a POSA would have selected linezolid as a lead compound because (1) it was the most advanced oxazolidinone in Phase III clinical trials; (2) linezolid had an excellent pharmacokinetic profile, specifically 100% bioavailability; and (3) linezolid possessed structural motifs characteristic of existing Factor Xa inhibitors.

At the onset, the court noted that there were seven attractive lead compounds in the Factor Xa field at the time of the invention; that group did not include linezolid. A POSA would have been motivated to choose one of the seven compounds with known Factor Xa activity. Further, the court explained that the prior art taught away from the selection of linezolid as the lead compound. Linezolid had no activity against Factor Xa, had several adverse effects and toxicities, and had a potent antibacterial effect, which would have promoted antibiotic resistance.

Addressing the defendants' arguments, the court first noted that linezolid was in clinical trials for antibiotic indications rather than Factor Xa indications and there was no evidence in the prior art that oxazolidinones were useful as Factor Xa inhibitors. The court also found that 100% bioavailability, by

itself, was an insufficient reason to choose linezolid as a lead compound. A high degree of bioavailability is meaningless without known activity against Factor Xa. Finally, the court found that that linezolid did not have structural motifs characteristic of Factor Xa inhibitors. In particular, the prior art taught using a pyrrolidinone scaffold rather than an oxazolidinone scaffold and provided no reason to swap the scaffold. Therefore, the court found that a POSA would not have chosen linezolid as a lead compound.

Under the second prong of the lead-compound analysis, the court found that even if a POSA would have been motivated to choose linezolid as a lead compound, a POSA would not have made the modifications necessary to arrive at rivaroxaban. First, a POSA would have modified linezolid's oxazolidinone core by replacing it with a known Factor Xa inhibitor in an effort to eliminate linezolid's antibacterial activity. Modification of the core would not have led to the development of rivaroxaban. Further, a POSA would not have made two structural modifications required to develop rivaroxaban because they were not supported in the prior art and contrary to conventional wisdom.

Finally, the court analyzed secondary considerations of nonobviousness. It found that rivaroxaban satisfied a long-felt but unmet need as evidenced by 18 pharmaceutical companies and hundreds of scientists researching Factor Xa inhibitors. The court also found that rivaroxaban had success where others failed, received substantial industry praise, had industry skepticism, is accepted by the medical community, and demonstrated unexpected properties. Overall, Xarelto is a "blockbuster commercial success." The court found a nexus between the secondary considerations and the claimed invention because the asserted claim covers rivaroxaban, the sole active ingredient in Xarelto. Therefore, the secondary considerations weighed in favor of nonobviousness.

PATENTS / INFRINGEMENT

James J. Kritsas

Amgen Patent Claims Do Not Cover Products with Additional Ingredients Not Listed in the Claims

Amgen Inc. v. Amneal Pharm. LLC (D. Del. 2018)

Following a four-day bench trial in a consolidated patent infringement action brought by Amgen, the US District Court for the District of Delaware found Amneal, Watson, and Piramal did not infringe Amgen's patent, but that Zydus's proposed ANDA did infringe. The court construed the claims directed to a pharmaceutical composition as being "closed to unrecited binders and disintegrants" and found that "there could be no literal infringement if the Defendants' ANDA product contained an unrecited (or unlisted) binder or disintegrant." *Amgen Inc. v. Amneal Pharm. LLC*, 328 F. Supp. 3d 373, 386 (D. Del. 2018) (Goldberg, J.).

Amgen listed the asserted patent in the FDA's Orange Book in connection with Sensipar (cinacalcet HCL), a treatment for secondary hyperparathyroidism. Claim 1 of the patent recites a pharmaceutical composition combining Markush groups of specific excipients, namely, a diluent, a binder, and a disintegrant, in specific amounts, with the active ingredient cinacalcet HCl. Amgen accused defendants Amneal, Watson, Piramal, and Zydus of infringing its patent by filing ANDAs seeking FDA approval to manufacture, use, and/or sell generic versions of Sensipar. The court bifurcated the infringement claims and invalidity counterclaims for trial, and held a four-day bench trial on infringement.

Amneal

The court found that Amneal's ANDA did not infringe the binder and disintegrant claim limitations. Amneal's ANDA uses Opadry as its binder, which is not listed in the '405 patent's Markush group for binders. Amgen argued that Opadry is a pseudonym for hydroxypropyl methylcellulose (HPMC), which is a listed binder, and, alternatively, that Amneal's ANDA infringes under the doctrine of equivalents. Crediting Amneal's expert, the court found that a POSA would not consider Opadry and HPMC synonymous because they have "different chemical structures, physical characteristics, binding mechanisms, and commercial sources." With respect to the doctrine of equivalents argument, the court found Amgen's expert's opinion conclusory: "Amgen's expert, Dr. Davies, never once used the word 'function,' 'way,' 'result,' or 'substantial/insubstantial differences.' Nor did he provide particularized testimony on each point of comparison, given without explanation or corroborating evidence, and thus persuasive."

Additionally, Amneal's ANDA discloses the use of an unlisted disintegrant (pregelatinized starch). Amgen argued that the pregelatinized starch in Amneal's product was functioning not as a disintegrant, but as a diluent that *was* listed. The court rejected this argument because Amneal's expert explained that Amneal's ANDA product did not need another diluent; its manufacturing process ran contrary to Amgen's expert's opinion; and the ANDA included testing that showed the pregelatinized starch in Amneal's product functioned as a disintegrant.

Watson

The court next found that Watson's ANDA did not infringe the '405 patent because it lists an unlisted disintegrant, low substituted hydroxypropyl cellulose (L-HPC), in its formulation. The court analyzed Amgen's infringement arguments under both the function-way-result test and the insubstantial differences test. As it had with Amneal, the court found that Amgen's expert did not identify at trial what he considered to be the function, way, or result of the disintegrants being compared and failed to meet Amgen's burden of proving infringement. Similarly, Amgen's expert

did not provide an opinion regarding the insubstantial differences between L-HPC and the listed disintegrant.

Piramal

With respect to Piramal, Amgen argued that the unlisted binder in Piramal's ANDA product—pregelatinized starch—has two components: a native starch fraction that functions as a diluent; and a cold-water soluble fraction that functions as a binder. Neither pregelatinized starch nor its cold-water soluble fraction is listed in the Markush group for binders. Therefore, Amgen argued that a cold-water soluble fraction is equivalent to povidone. The court, however, found that Amgen was foreclosed by prosecution history estoppel from asserting the doctrine of equivalents against Piramal's use of pregelatinized starch as a binder.

Zydus

Finally, the court held that Zydus's ANDA product literally infringed claim 1 of the '405 patent. The dispute boiled down to the function of pregelatinized starch, which was listed as a diluent in Zydyus's ANDA. Zydus took the position that the pregelatinized starch functions as a binder, which was the same opinion that Amgen's expert asserted in its infringement argument against other defendants. "Thus, we are in a counterintuitive world where Amgen wins against Zydus only if the opinion of Amgen's expert—which Amgen relies on to prove infringement against the other defendants—is unpersuasive." As noted above, the court rejected Amgen's expert's opinion regarding pregelatinized starch, finding it acted as a diluent. Because Amgen had not proven by a preponderance of the evidence that pregelatinized starch should be artificially divided into two fractions, with each fraction alone serving a different function, the court held that Zydus's ANDA product literally infringed.

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