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ANDA Update

Table of Contents

ON-SALE BAR

On-Sale Bar Is No Bar for Selling Manufacturing Services to the Inventor

The Medicines Company v. Hospira, Inc. (Fed. Cir. July 11, 2016)

Bhanu K. Sadasivan, PhD

Addressing what constitutes an invalidating "sale" under § 102(b), the US Court of Appeals for the Federal Circuit sitting *en banc* affirmed the lower court's ruling and concluded that a third-party manufacturer's sale to the inventor of services to manufacture the product, where title to the product never passed to the manufacturer, does not constitute an invalidating sale under § 102(b). *The Medicines Company v. Hospira, Inc.*, 119 U.S.P.Q.2d 1329 (Fed. Cir., July 11, 2016) (O'Malley, J.)

The case concerned whether the on-sale bar was triggered when The Medicines Company (MedCo) paid a third-party contract manufacturer, Ben Venue, to manufacture improved Angiomax® (bivalirudin), the brand name drug that is an embodiment of the patented claims before the critical date. MedCo does not have its own manufacturing facilities and cannot make its products in-house. MedCo therefore contracted with Ben Venue to make commercially saleable improved Angiomax. The transaction was confidential in nature, and title to the Angiomax batches was never transferred to Ben Venue.

To trigger the on-sale bar, the claimed invention must be (1) the subject of a commercial offer of sale and (2) ready for patenting. *Pfaff v.Wells Electronics, Inc*., 525 US 55 (1998). Applying the *Pfaff* framework, the district court determined that Ben Venue's manufacture of Angiomax did not trigger the on-sale bar because step one of *Pfaff* was not met, although step two was met. The district court explained that the title to Angiomax always resided with MedCo and that the batches of Angiomax made by Ben Venue were for experimental purposes, and not for commercial profit.

On appeal, Hospira argued that any transaction that provides a commercial benefit to the inventor, in this case by stockpiling its product for future sale, was sufficient to trigger the on-sale bar. The lack of transfer of title to Angiomax was irrelevant, according to Hospira, because the stockpiling provided financial benefit to constitute "commercialization" or "commercial exploitation" to thereby trigger the on-sale bar. A panel of the US Court of Appeals for the Federal Circuit agreed with Hospira focusing on the commercial exploitation of the invention before the critical date and the lack of experimental use because the invention had been reduced to practice, and reversed the lower court's ruling.

Sitting *en banc*, the Federal Circuit reversed the panel ruling and concluded that the Ben Venue's manufacture of the Angiomax batches before the critical date was not a commercial sale of the invention under step one of the *Pfaff* framework. The court did not address the question of experimental use in step one of *Pfaff* or address step two of *Pfaff*.

The court explained that in determining whether a sale or offer for sale of an invention is commercial in nature, the focus should be on activities that would be understood to be commercial sales or offers for sale "in the commercial community" and that the Uniform Commercial Code (UCC) is an appropriate avenue to determine whether the transaction rises to the level of a commercial transaction. However, the court cautioned that "the UCC does not have 'talismatic significance' with respect to the on-sale bar," noting that an invention may be considered on-sale where the inventor charges the user fee to use the invention, but no title is passed. Nonetheless, the absence of transfer of title is a significant factor to consider, the court explained, because in most instances it "indicates an absence of commercial marketing of the product by the inventor."

The court also addressed other factors that could influence the determination of a "commercial" sale. The confidential nature of the transaction, although not of talismatic significance, can weigh against the commercial nature of a transaction, the court concluded. Likewise, the identity of the participants is not key, the focus must be on the commercial nature of the transaction. A sale made by a supplier does not stop being a commercial transaction merely because the sale is made by a supplier, *i.e.*, there is no 'supplier exception' to the on-sale bar. "Where the supplier has title to the patented product or process, the supplier receives blanket authority to market the product or disclose the process for manufacturing the product to others, or the transaction is a sale of product at full market value, even a transfer of product to the inventor may constitute a commercial sale under § 102(b)."

The court further clarified that "not every activity that inures some commercial benefit to the inventor can be considered a commercial sale," rejecting Hospira's argument to the contrary. "It is well-settled that mere preparations for commercial sales are not themselves 'commercial sales' or 'commercial offers for sale' under the on-sale bar."

In the case at bar, the court determined that the invention at issue was a product, Angiomax, not a method of making the product. "[W]e have never espoused the notion that, where the patent is to a product, the performance of the unclaimed process of creating the product, without an accompanying "commercial sale" of the product itself, triggers the on-sale bar." The court concluded that Ben Venue sold "manufacturing services—not the patented invention—to MedCo" and therefore "there was no sale of the invention." The court also noted that the absence of transfer of title to Angiomax batches and the scope and nature of the confidentiality imposed on Ben Venue further underscored that the sale was for manufacturing services and was not for commercial marketing purposes. The court also rejected Hospira's "stockpiling" argument finding that "mere stockpiling of a patented invention by the purchaser of manufacturing services does not constitute a 'commercial sale' under § 102(b). Stockpiling—or building inventory—is, when not accompanied by an actual sale or offer for sale of the invention, mere pre-commercial activity in preparation for future sale."

The court further noted that there was no justification to apply a different set of on-sale bar rules depending on whether the inventor manufactures the product in-house or outsources it. "Yet, penalizing a company for relying, by choice or by necessity, on the confidential services of a contract manufacturer, does exactly that."

PRACTICE NOTE

Do not assume that the nature of the transaction, from supplier to inventor, its confidentiality nature or the lack of transfer of title will automatically prevent on-sale bar. The specific activities and the nature of the invention matter.

INFRINGEMENT

Infringement under the Doctrine of Equivalents

Intendis GMBH v. Glenmark Pharmaceuticals Inc. (Fed. Cir. May 16, 2016)

Shon Lo

The US Court of Appeals for the Federal Circuit affirmed the finding of infringement from the US District Court for the District of Delaware under the doctrine of equivalents based on admissions from the defendant's abbreviated new drug application (ANDA). *Intendis GMBH v. Glenmark Pharmaceuticals Inc., USA,* 822 F.3d 1355 (2015) (Moore, C.J.)

At issue was whether Glenmark's design-around formulation infringed Intendis' *Orange Book*-listed formulation patent (US No. 6,534,070) for Finacea® Gel (azelaic acid) under the doctrine of equivalents. The patent claims required the presence of at least one triglyceride and lecithin in the azelaic acid formulation. The issue was whether isopropyl myristate in Glenmark's generic product performed the same function as the two required excipients under the doctrine of equivalents. The district court found equivalency under the function-way-result test, relying on expert testimony, support in the scientific literature and statements in Glemark's ANDA and patent application.

Glenmark argued on appeal that (1) Intendis failed to prove the claimed excipients functioned as penetration enhancers because the '070 patent did not disclose this function, and (2) that the district court erred in finding isopropyl myristate functioned as a penetration enhancer in Glenmark's formulation. Even though the '070 patent did not disclose that triglycerides and lecithin function as penetration enhancers, the Federal Circuit noted that it has "never held that a patent must spell out a claim element's function, way, and result in order for the doctrine of equivalents to apply as to that element." Rather, "when the claims and specification of a patent are silent as to the result of a claim limitation," courts should "turn to the ordinary skilled artisan." Thus, fact finders may rely on extrinsic evidence to determine how a claim element functions. Here, the key extrinsic evidence was Glenmark's statements in its own ANDA submission that repeatedly referred to the excipients in question as penetration enhancers.

The Federal Circuit also affirmed the district court's hypothetical claim analysis on whether the equivalents would impermissibly ensnare the prior art. The court determined the hypothetical claim adopted by the district court was proper in scope, rejecting Glenmark's argument that the hypothetical claim must capture all penetration enhancers, not just isopropyl myristate.

Finally, the Federal Circuit found no error in the district court's finding that prosecution history estoppel did not bar the application of the doctrine of equivalents to the claim elements in question. The amendment in question concerned revision of lecithin concentrations in two dependent claims from the range of "up to 1%" and "up to 3%" to "from more than 0 to 1%" and "from more than 0 to 3%." These claims depended from independent claims that required lecithin. Reasoning that dependent claims can never be broader than the independent claim from which they depend, the dependent claims as originally written could not have included zero percent lecithin formulations, and thus patentees did not disclaim lecithin-free formulations.

INDUCED INFRINGEMENT

Hikma Successfully Moves to Dismiss Takeda's Induced Infringement Claims after Commercially Launching Its Mitigare® Drug for the Prevention of Gout Flares

Takeda Pharmas. v. West-Ward Pharma. Corp. (D. Del. May 18, 2016)

Jeffrey R. Gargano

Upon remand from the US Court of Appeals for the Federal Circuit, the US District Court for the District of Delaware dismissed Takeda's claim of induced infringement, finding that the mere existence of direct infringement by physicians is not sufficient to support a claim of inducement. Instead, the accused infringer, Hikma, must encourage, recommend or promote infringement. *Takeda Pharmas. v. West-Ward Pharma. Corp.,* 2016 WL 2904593 (D. Del., May 18, 2016) (Robinson, J.)

Takeda markets a colchicine drug product, Colcrys®, which was approved for the two separate indications of use: (1) prophylaxis of acute gout flares and (2) treatment of acute gout flares. Takeda is also the owner of several patents covering methods of use of its colchicine drug product, Colcrys. Hikma received FDA approval of the accused product, Mitigare®, under the Section 505(b)(2) pathway of the Hatch-Waxman Act, carving out of its label the uses for which Takeda has patent protection. Hikma's Mitigare product was indicated for prophylaxis of gout flares in adults only. Upon launch of Hikma's Mitigare product, Takeda moved for a temporary restraining order, which the court granted. Takeda then moved for a preliminary injunction. The court reviewed Takeda's preliminary injunction motion and concluded that because Takeda has failed to demonstrate that it will likely prove induced infringement at trial or suffer irreparable harm, the extraordinary relief of a preliminary injunction is not warranted. Takeda appealed. The Federal Circuit affirmed the denial of Takeda's motion for a preliminary injunction and remanded the case back to the District Court of Delaware whereby Hikma moved to dismiss Takeda's claims of induced infringement under Fed. R. Civ. P. 12(b)(6).

In its complaint, Takeda alleged that Hikma's Mitigare products induced infringement of its patents directed to the treatment of acute gout flares. To support its claim of induced infringement, Takeda relied primarily on: (1) the Mitigare product labels; (2) Hikma's correspondence with the US Food and Drug Administration (FDA); and (3) Hikma's sales and marketing activities. Takeda pointed out that the same 0.6 milligrams of colchicine can be used for either prophylaxis or treatment of gout flares and the Mitigare label instructs patients, "If you have a gout flare while taking Mitigare, tell your healthcare provider." Takeda asserted that this instruction means that health care providers will prescribe Mitigare products for the treatment of acute gout flares according to the Colcrys product label and guidelines. As for the Hikma FDA correspondence, Takeda alleged that the FDA informed Hikma if Mitigare is being used for prophylaxis, it may be natural for the provider to use it for acute treatment as well. Takeda also contended that Hikma entered into at least two "sole-source contracts" with insurance providers that effectively guarantee for all patients covered by these insurance providers the only colchicine option available to them for the treatment of acute gout flares will be Hikma's Mitigare product.

Addressing the allegations regarding the Mitigare label first, the court found that the label was not a sufficient catalyst to constitute active steps taken to encourage direct infringement as it requires consultation with a health care provider "who may (or may not) consult the Colcrys prescribing information, and who may (or may not) follow the patented method of use for treatment of the acute gout flare." The court concluded this was an insufficient basis upon which to establish induced infringement. Next, the court found the allegations regarding third-party insurance providers "merely acknowledges potential infringement by others, not that Hikma has taken active steps to encourage direct infringement." Finally, the court noted that the allegations in Takeda's complaint stating Mitigare **can be used** for acute gout flares, including the FDA correspondence with Hikma, is not the same thing as stating Mitigare **should be used**, explaining how to infringe and showing patients follow those instructions. The court ultimately concluded that given the lack of factual allegations in the complaint, Takeda does not have a "plausible claim for relief" and granted Hikma's motion to dismiss.

INDIRECT INFRINGEMENT (CARVE OUT/SKINNY LABEL)

GSK Survived Teva's Third Motion to Dismiss Allegations of Indirect Infringement because of the Totality of Teva's Skinny Label

GlaxoSmithKline LLC, et al. v. Teva Pharmaceuticals USA, Inc. (D. Del. July 20, 2016)

Krista Vink Venegas, PhD

In this ongoing patent infringement case, Magistrate Judge Burke issued a report and recommendation to deny Teva's Rule 12(b)(6) motion to dismiss GlaxoSmithKline's (GSK) induced infringement allegations relating to generic product sales during a select time period (January 2008–May 2011). The magistrate determined that while Teva carved out the patented indication of use, other instructions in the generic product label plausibly evidence Teva's intent to induce infringement of the patented methods. *GlaxoSmithKline LLc, et al. v. Teva Pharmaceuticals USA, Inc.*, Case No. 14-cv-0878, slip op. July 20, 2016 (D. Delaware, Magistrate Judge Christopher J. Burke)

In 2014, GSK filed this patent infringement action relating to the active ingredient carvedilol (Coreg®) which was initially identified for the treatment of hypertension. Coreg® then became the first beta blocker the US Food and Drug Administration (FDA) approved for the treatment of congestive heart failure (CHF) after observation that the long term use reduced mortality in CHF patients. Coreg® was initially approved in 1997 for treatment of mild-to-moderate CHF in conjunction with other therapies, and subsequently in 2001 was approved for treatment of mild-to-severe CHF. Although initially contraindicated for heart attack patients, in 2003, GSK obtained an expanded indication for these patients based on positive clinical studies. Thus, the Coreg® label includes three indications relating to use for: hypertension, mild-to-severe CHF and heart dysfunction after heart attack.

Teva filed an abbreviated new drug application (ANDA) in 2002, submitting a Paragraph IV certification of invalidity against the then-*Orange Book*-listed '069 patent method of treatment claims. The '069 patent was later reissued and relisted by GSK as the '000 patent. In 2007, Teva submitted an amended ANDA including a Section VIII carve out for the indication of use for the treatment of mild-to-severe CHF. Teva obtained FDA approval in 2007 based on the skinny label (lacking the mild-to-severe CHF indication) and the labelling remained the same until 2011.

In this suit, GSK's complaint initially asserted indirect infringement allegations against generic filers Teva and Glenmark for the method of treatment claims of the '000 patent. Teva and Glenmark successfully moved to dismiss these original allegations, as well as allegations indirect infringement allegations in GSK's first amended complaint because Teva's label carved out the indication for the treatment of mild-to-severe CHF (pre-2011). Although Teva's motion was granted, the court granted GSK leave to amend its pleadings, and GSK filed *second amended* complaint alleging indirect infringement of the '011 patent based on Teva's pre-2011 product sales. Teva filed another motion to dismiss claims relating to pre-2011 carvedilol product sales.

In considering the present motion to dismiss, the magistrate judge applied the Rule 12(b)(6) pleading standards to this case inquiring whether GSK's second amended complaint plead facts plausibly showing that in spite of its carve out, "Teva specifically intended third parties to infringe the '000 patent and knew that the third party's acts constituted infringement." Teva contended that GSK failed to state facts showing Teva's specific intent to induce or knowledge of infringement, although GSK alleged that Teva actively publicized the "AB-rating" for generic carvedilol without highlighting that its product was not approved for all of the same indications as Coreg®.

The magistrate found GSK's allegations that Teva was promoting its product as AB-rated alone was not sufficient to make out a claim for inducement at least because: (1) the *Orange Book* explains that an AB-rating means that the product is therapeutically equivalent to the brand product, but *only for the conditions or uses specified in the labeling for the generic product*, and in view of that explanation; (2) it cannot be assumed that third parties will necessarily mistake the generic product for being fully-substitutable; or that (3) Teva had the intent for third parties to be mistaken. However, the court found "a small piece of intent" in GSK's allegations that Teva's press releases evidenced an intent to capture sales for *all* therapeutic uses of the generic product because Teva's press releases referenced the total annual sales of Coreg®, which included sales for treatment of CHF. More significantly, the court found GSK's allegations relating to Teva's labelling may indicate the plausibility that Teva specifically intended third parties to infringe the '011 patent. Specifically, the Coreg® indication of use for heart dysfunction after heart attack (included in Teva's label) is drafted such that it includes reference to CHF patients, such as: "Carvedilol tablets are indicated to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤40% (*with or without symptomatic heart failure*)" (emphasis added, citing also to language in the clinical studies, "heart failure/fluid retention" adverse event and patient advise sections referencing "heart failure"). The magistrate's analysis analogized the facts in this case to the Federal Circuit's decision in *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042 (Fed. Cir. 2010). In that case the generic manufacturer's approved labeling included an indication for a non-patented twice-daily use, but instructions on dose titration could lead to a once-daily dose that was patented. In *AstraZeneca*, the court found the "pertinent question is whether the proposed label instructs users to perform the patented method [if it does then]

the proposed label may provide evidence of [a generic manufacturer's] affirmative intent to induce infringement." Here, the court determined that it was plausible that in spite of Teva's carve out, the broader labeling and instructions may be viewed as an encouraging consumers to infringe the '000 patent because there is a relationship between the two patient populations—heart attack patients may also be CFH patients—as the labelling suggests.

Finally, the magistrate found further support of Teva's inferred intent to induce infringement in the fact that allegedly there are not substantial non-infringing uses for Coreg®. Specifically, Teva was aware that: (1) GSK has marketed the product in the United States only for treatment of CHF and (2) uses for the other approved indications are purportedly minimal.

Therefore, the magistrate found GSK's pleaded facts sufficient to survive Teva's Rule 12(b)(6) challenge and recommended that the District Court deny Teva's motion. On August 25, 2016, Teva filed a memorandum in opposition to the magistrate's report and recommendation. Trial is scheduled to begin in this case on June 12, 2017.

LIMITS OF SECTION 271(E)(2)

Section 271(e)(2) Only Applies to Patents That Have Issued as of the ANDA Filing Date

Ferring B.V. v. Actavis, Inc. (D.N.J. May 26, 2016)

Lauren Martin

Addressing for the first time the issue of whether §271(e)(2) applies to a patent that issued years after an abbreviated new drug application (ANDA) was approved, the US District Court for the District of New Jersey granted Defendants' motion to dismiss pursuant to Rule 12(b)(6). *Ferring B.V. v. Actavis, Inc.*, Case No. 15-4222 (D.N.J. May 26, 2016) (Chesler, J.)

Plaintiffs filed a complaint in June 2015 alleging that Defendants' generic version of their Lysteda® product infringed a formulation patent that issued in January 2015. In addition to asserting infringement under §271(a) for the sale of Defendants' product (the ANDA was approved in 2012), Plaintiffs also alleged that the filing of the ANDA in 2010 constituted infringement of the January 2015 patent under §271(e)(2). Defendants filed a motion to dismiss the §271(e)(2) claim under Rule 12(b)(1) for lack of subject matter jurisdiction or Rule 12(b)(6) for failure to state a claim. The court granted Defendants' motion and dismissed the claim pursuant to Rule 12(b)(6).

The court rejected Defendants' argument for lack of subject matter jurisdiction, finding that Plaintiffs satisfied the low threshold necessary to meet the requirement. As the court explained, the patentee need only allege that "another's filing of an ANDA infringes its patent under § 271(e)(2)." Thus, the subject matter jurisdiction requirement was met by virtue of Plaintiffs' allegation that Defendants' ANDA infringed the asserted patent.

Next, the court turned to the question of whether Plaintiffs' §271(e)(2) claim passed muster under Rule 12(b)(6), and concluded that it did not. The court found that Plaintiffs' claim was inconsistent with the statutory text, which establishes that it "shall be an act of infringement to submit [an ANDA] for a drug *claimed in a patent*…." According to the court, the "inclusion of the phrase 'claimed in a patent' in the statute indicates that a § 271(e)(2)(A) claim must be based upon a patent that has already been issued at the time the infringing ANDA is filed."

Furthermore, in view of the facts pled, allowing a claim under §271(e)(2) would contradict the purpose of the statute. Section 271(e)(2) "provides patentees with a defined act of infringement sufficient to create case or controversy jurisdiction to enable a court to promptly resolve any dispute concerning infringement and validity when the ANDA applicant was not making, using, or selling the patented product." Plaintiffs "no longer need an artificial act of infringement claim under § 271(e)(2)(A) to enforce their patent rights." Rather, Plaintiffs can (and did) "bring actual infringement claims against Defendants under §271(a), based on Defendants' alleged marketing of a generic version of Lysted®."

PRACTICE NOTE

Patents that issue after an ANDA is filed cannot serve as the basis for an infringement claim under §271(e)(2).

ANTITRUST

Northern District of California Dismisses Claims that Gilead Violated the Antitrust Laws in Seeking to Protect its Position on HIV Drug

AIDS Healthcare Foundation, Inc. v. Gilead Sciences (N.D. Cal. July 6, 2016)

William Díaz

Ruling on a motion to dismiss, the US District Court for the Northern District of California dismissed AIDS Healthcare's antitrust claims alleging that Gilead Sciences illegally tied and bundled its human immunodeficiency virus (HIV) drug, tenofovir alafenamide fumarate (TAF) with other drugs and sought to maintain its monopoly in the TAF market. The decision is notable because the court concluded that AIDS Healthcare's illegal tying claims could not stand because Gilead did not have US Food and Drug Administration (FDA) approval for standalone TAF and, thus, could not have tied its sales to that of another product. *AIDS Healthcare Foundation, Inc. v. Gilead Sciences, Inc., et al.* (N.D. Cal. July 6, 2016) (Alsup, W.)

In 2015, Gilead sought FDA approval for three new combination drugs used to treat HIV—Genvoya®, Descovy® and Odefsey®—each of which consisted of TAF combined with other drugs. At the time, Gilead did not seek FDA approval for a standalone version of TAF. The FDA approved Genvoya in November 2015 and the other two drugs shortly thereafter, and granted Gilead a five-year new chemical entity (NCE) exclusivity period over any product containing TAF. Accordingly, no generic drug containing TAF can receive FDA approval until November 2020. In the first quarter of 2016, Gilead applied for FDA approval of a standalone version of TAF and anticipates FDA approval in November 2016.

AIDS Healthcare's complaint alleged that Gilead and co-defendants Johnson & Johnson, Janssen Sciences Ireland UC and Japan Tobacco violated federal, California and Nevada antitrust laws. The complaint alleged that Gilead illegally tied and bundled TAF to sales of products sold by the other defendants by combining them into fixed-dose combination drugs Genvoya, Descovy and Odefsey.

The first element of a tying claim is the existence of two distinct products in different markets whose sales are tied together. In dismissing this claim, the court held that even though there may be consumer demand for standalone TAF, because the product does not have FDA approval, "[t]he extent of consumer demand for standalone TAF is irrelevant because TAF *cannot* be sold as a standalone product as a matter of law….As such AIDS Healthcare has failed to plead the existence of a market for a tying product…"

In its monopolization claim, AIDS Healthcare alleged that "by bundling TAF with the other ingredients, [Gilead] insulated the allegedly weak patents covering TAF from challenges, because any generic manufacturer seeking to produce a TAF product would need to invalidate all the patents listed in the *Orange Book* for those drugs before it could win FDA approval, rather than just the TAF patents." The court dismissed this claim for several reasons. First, AIDS Healthcare alleged that Gilead had monopoly power over TAF-containing drugs but did not allege any facts to support its market definition. Second, AIDS Healthcare failed to allege that Gilead engaged in anticompetitive conduct, and the court noted that even a monopolist has a right to decide when to bring its products to market. Finally, the court stated that Gilead expects FDA approval on standalone TAF in November 2016 and, thus, "Gilead has already taken steps to expose the alleged vulnerabilities of the patents protecting TAF several years before its NCE exclusivity would expire and the first possible generic TAF products can enter the market."

The court also dismissed AIDS Healthcare's conspiracy and state antitrust claims for largely the same reasons that it relied on to dismiss its tying and monopolization claims. AIDS Healthcare's complaint also brought a claim for declaratory judgment of patent invalidity, which the court dismissed as well. AIDS Healthcare has appealed the court's ruling on the motion to dismiss to the Federal Circuit.

INVALIDITY/OBVIOUSNESS

Post-Trial Findings – Not So Obvious

Bayer Pharmaceuticals AG et al. v. Watson Laboratories, Inc. et al. (D. Del. April 27, 2016)

Avani C. Macaluso

Upholding the validity of Bayer's patent covering orally disintegrating tablet (ODT) formulations of vardenafil hydrochloride trihydrate, the US District Court for the District of Delaware rejected Defendant's arguments that the claims were invalid as obvious. Notwithstanding, the court also held the secondary objective *indicia* points to non-obviousness. *Bayer Pharmaceuticals AG et al. v. Watson Laboratories, Inc. et al.*, C.A. No. 12-cv-517, 2016 WL 1703281(D. Del. April 27, 2016)

At issue was Bayer's US Patent No. 8,613,950, directed to particular orally disintegrating tablet formulations of vardenafil hydrochloride trihydrate. Specifically, Claim 9 is directed to a drug formulation wherein the sugar alcohols are a mixture of sorbitol and mannitol. Claim 11 is directed to a drug formulation wherein at least one sugar alcohol is sorbitol. Bayer received approval from the US Food and Drug Administration (FDA) to market vardenafil hydrochloride orally disintegrating tablets (ODT), 10 milligrams, under the trade name Staxyn® for the treatment of erectile dysfunction. Watson sent Bayer a Paragraph IV notice letter indicating it submitted an abbreviated new drug application (ANDA) seeking approval for 10 milligram vardenafil hydrochloride orally disintegrating tablets, prior to the expiration of the *Orange Book*-listed patents.

Bayer brought suit against Watson alleging infringement under the Hatch-Waxman Act. It filed two separates lawsuits—one on April 25, 2012, alleging infringement of the US Patent Nos. 6,362,178 and 7,696,206 and the second on March 21, 2014, for infringement of the '950 patent. Both actions were consolidated for trial. The parties stipulated to infringement of the asserted claims of the '178 and '206 patents, provided the claims are valid and enforceable. After a six-day bench trial, the court rejected Watson's indefiniteness defense and ruled that the asserted claims of the '178 and '206 were not obvious. During post-trial briefing, the parties stipulated to infringement of the '950 patent, leaving the only remaining issue, Watson's obviousness defense with respect to the '950 patent.

Watson argued that the asserted claims for the '950 patent are obvious for two reasons: (1) combining vardenafil hydrochloride trihydrate with the sugar alcohol excipients mannitol and sorbitol into a known ODT dosage form was taught by the prior art and would have be obvious to a person of ordinary skill in the relevant art (POSA); and (2) competitive pressure would have motivated a POSA to derive the claimed subject matter. Relying on Bayer's expert, the court determined that absent hindsight, there was no motivation in the prior art to develop vardenafil ODT because of the rarity of ODT formulations. The court found significant that prior art references from 2004 listing ODTs on the market, and likely to come to market in the next few years, did not include any drugs for the treatment of erectile dysfunction.

The court also considered whether a POSA would have been motivated to make an immediate-release ODT, rather than a delayed release ODT focusing on concerns related to increased bioavailability and taste. Bayer contended that immediate release ODT results in increased bioavailability of vardenafil, a major concern in older men. Additionally, a POSA would have expected vardenafil would have a bitter taste and therefore taught away from developing an ODT. Both of these concerns taught away from the claimed subject matter. Finally, the court determined that there was nothing in the prior art that would have given a POSA reason to use sorbitol and mannitol in an ODT, and that the tableting properties of mannitol and sorbitol mixtures are not obvious. The court relied on Bayer's evidence that every ODT on the market in the relevant time frame contained only a single sugar alcohol—mannitol.

The court was further persuaded by several secondary considerations that weigh against a finding of obviousness, holding the bioavailability profile would have been unexpected by a POSA at the time. Specifically, a POSA making an ODT formulation of vardenfil would have wanted to formulate the ODT similar to Levitra® (another vardenfil formulation for the treatment of erectile dysfunction). Bayer states that a POSA would not have expected the bioavailability curves for Staxyn compared to Levitra to have an increase in bioavailability and no increase in the maximum concentration of vardenafil in the bloodstream. Staxyn's results lead to a longer duration of action without added side effects. The court also agreed that Watson's copying is evidence of non-obviousness. Typically, copying is not relevant in the ANDA context, however here, Bayer demonstrated that Watson did not simply copy in order to bring the Paragraph IV

challenge, but desired the claimed subject matter. In support, Bayer proffered evidence that Watson considered design-arounds, but instead copied Bayer's formulation.

Watson's request for attorneys' fees was denied having held the in favor of Bayer on the issue of obviousness.

ANTITRUST

Massachusetts Court Weighs in on Product Hopping Allegations and Reverse Payment Standing

In re Asacol Antitrust Litigation (D. Mass. July 20, 2016)

Alex M. Grabowski

Addressing a motion to dismiss a bevy of antitrust allegations, the US District Court for the District of Massachusetts held that a class of purchasers had sufficiently pled allegations of "hard switch" product hopping. However, the court also held that the purchasers did not have standing to assert a claim for an allegedly anticompetitive reverse-payment settlement. *In re Asacol Antitrust Litigation*, 15-cv-12730 (Jul. 20, 2016) (Casper, J.)

The case related to the drugs Asacol®, Asacol HD® and Delzicol®, a family of drugs marketed by Warner Chilcott (now a subsidiary of Actavis) for the treatment of ulcerative colitis, an inflammatory bowel disorder. All three medications contain the same active ingredient, mesalamine. Asacol is a treatment approved to manage mild to moderately active ulcerative colitis, as well as a maintenance therapy for patients whose ulcerative colitis is in remission. Asacol HD is a higher dose of mesalamine, approved only for the treatment of moderately active ulcerative colitis. Delzicol is a redesigned version of Asacol that is identical except for a change in the outer capsule, which is covered by its own patent. Two separate sets of activities surrounding these medications give rise to the antitrust claims in this case.

Product Hopping Claims

The product hopping claim stems from Warner Chilcott's decision to remove Asacol from the market shortly before its patent expiration and begin marketing Delzicol. Warner Chilcott asserted that this decision was based on guidance from the US Food and Drug Administration (FDA) about the dangers of dibutyl phthalate, a substance present in the coating of Asacol, but not Delzicol. The purchasers alleged that this was a pretext for pulling Asacol from shelves to destroy the market before generic entry.

The court ultimately decided that the purchasers had sufficiently pled a claim for monopolization under §2 of the Sherman Act. The purchasers asserted that Warner Chilcott possessed monopoly power in the mesalamine market and that pulling Asacol from the market was an improper attempt to maintain that power. Warner Chilcott put forward three arguments to the contrary, but the court was not convinced.

First, Warner Chilcott argued that its rationale for pulling Asacol based on FDA guidance should insulate it from antitrust claims. However, the purchasers sufficiently pled pretext allegations because the guidance was non-binding and did not justify completely pulling Asacol from the market and because Warner Chilcott continued to use it elsewhere.

Second, Warner Chilcott argued that the innovation represented by the patent covering Delzicol is inherently valuable to the public and thus should not trigger antitrust scrutiny. Despite this, the court held that there were plausible allegations that Warner Chilcott was using the patent not just for the limited monopoly it granted, but to extend its exclusivity period for its ulcerative colitis medication generally.

Finally, Warner Chilcott argued that its actions were a mere redesign of its product, which is consistent with competition. The court acknowledged that a healthy skepticism surrounds claims that a dominant firm's product redesign was anti-competitive. Yet, the court still allowed the claim to proceed based on the unique circumstances of the pharmaceutical industry. The redesign removed Asacol from the marketplace, preventing generic substitution by pharmacists, which would have a significant impact on the market for generic Asacol.

Reverse Payment Claims

The reverse payment claims arose from separate litigation between Warner Chilcott and Zydus Pharmaceuticals related to an abbreviated new drug application (ANDA) Zydus filed for Asacol HD. The case ultimately settled under an agreement

that gave Zydus two potential options for entering the market. First, Zydus could enter the market on November 15, 2015, with its own generic, provided that the FDA had approved Zydus' ANDA by then. Zydus would have to pay Warner Chilcott a 25 percent royalty of its net sales, and Warner Chilcott would maintain the right to supply an authorized generic to another company. Alternatively, if the FDA did not approve the ANDA, Zydus would be allowed to sell an authorized generic starting on July 2, 2016. In exchange, Zydus would pay 75 percent of its profits to Warner Chilcott. As of the opinion's publication, Zydus' ANDA remains unapproved. The purchasers asserted that this settlement agreement amounted to an impermissible delay of Zydus' entry into the market.

The court did not reach the issue of whether the pleading could survive a motion for failure to state a claim. Instead it held that the purchasers did not have standing to bring the claim. The court noted that the limiting factor for Zydus' entry into the market was not the settlement, but approval by the FDA. As such, the settlement could not be said to delay entry since Zydus would be unable to sell generic Asacol HD even in its absence. The purchasers argued that the settlement made Zydus less likely to push for FDA approval, but the court found that they had not offered any plausible allegations to support that argument.

HATCH-WAXMAN EXCLUSIVITY

Three-Year Exclusivity Bar Only Blocks Subsequent Applications for Drugs with the Same Active Moiety

Otsuka Pharmaceutical Co., Ltd. V. Burwell (D.D.C. July 28, 2016)

Mandy H. Kim

Addressing a question of statutory interpretation regarding the meaning of the applicable exclusivity provisions of the Federal Food, Drug, and Cosmetic Act (FDCA), the US District Court for the District of Columbia determined the US Food and Drug Administration (FDA) reasonably interpreted that the FDCA's three-year exclusivity bar blocks only subsequent applications for drugs with the same active moiety. *Otsuka Pharmaceutical Co., Ltd. V. Burwell*, Civil Action No. 15-1688 (D.D.C. July 28, 2016) (Jackson, J.)

In 2002, the FDA approved a new drug application by Otsuka for Abilify® tablets, an orally administered drug for the treatment of several mental disorders, including schizophrenia. The active moiety of Abilify tablets is the molecule aripiprazole, which is also the drug's active ingredient. Because the FDA had never before approved a drug with aripiprazole as its active moiety or ingredient, Abilify tablets received a five-year marketing exclusivity period that has since expired. In 2013, the FDA approved an application for another drug by Otsuka, Abilify Maintena®, which also has aripiprazole as its active moiety and ingredient. Abilify Maintena's novelty was that it is administered through extended-release injectable suspension rather than orally. Because Otsuka relied on new clinical investigations when it sought approval for Ability Maintena, it was entitled to an initial three-year marketing exclusivity period under 21 USC § 355(c)(3)(E)(iii). In 2014, the FDA approved a supplemental new drug application for Abilify Maintena that provided new clinical study results granting Abilify Maintena another separate three-year marketing exclusivity period under 21 USC § 355 (c)(3)(E)(iv).

In late 2014, Alkermes submitted a new drug application (NDA) under 21 USC § 355(b)(2) [(505(b)(2) Application)] for Aristada®, an extended-release injectable suspension formula for the treatment of schizophrenia (like Abilify Maintena). Aristada's active ingredient is aripiprazole lauroxil, a substance that metabolizes in the body into N-hydroxymethyl aripiprazole, which is Aristada's active moiety. Alkermes' Section 505(b)(2) Application relied on investigations Otsuka had sponsored with Abilify Tablets, but did not rely on any new clinical investigations Otsuka had undertaken with respect to Abilify Maintena. Rather, Alkermes conducted and submitted its own original studies to support its Section 505(b)(2) NDA for Aristada.

In 2015, Otsuka objected to Alkerme's Section 505(b)(2) Application for Aristada in a citizen petition that it filed with the FDA, arguing that the FDA was prohibited from approving Aristada prior to the expiration of the three-year exclusivity periods for Abilify Maintena because Aristada's 505(b)(2) Application was for the same conditions of approval, treated the condition in a similar way and relied on similar clinical trials (even though both the active ingredients and active moieties

were different). The FDA disagreed, stating that the FDCA's exclusivity provisions do not bar a second-in-time drug application if the drug with exclusivity and the drug for which approval is being sought have different active moieties. Otsuka filed the instant action against the FDA challenging the FDA's decision as "arbitrary and capricious" and in violation of the law. Otsuka also claimed that the FDA violated the notice and comment procedures.

Applying the two-step framework of *Chevron*, the district court found that the FDA's interpretation of the statute was reasonable. As to *Chevron*'s Step One, the court concluded that there were multiple plausible interpretations of the plain text of the bar clauses making these provisions ambiguous. Turning next to *Chevron*'s Step Two, the court found that the FDA's interpretation of the bar clauses was reasonable and permitted by the statutory text. In doing so, the court noted that for "approximately two decades now, the FDA has focused on the active moiety of a drug…to identify and distinguish different drugs." The court also explained that the FDA's interpretation was consistent with the relevant legislative history and policy considerations, namely that

> employing active moiety as a relevant criterion for determining whether a second-in-time application is barred promotes Hatch-Waxman's goals by protecting 'against approval of drugs with the same active moiety for the same exclusivity period use[,]' while simultaneously encouraging competition by ensuring that exclusivity could 'not block approval of drugs with different active moieties…that may have some advantages over previously approved active moieties.'

The court acknowledged Otsuka's claims that it may be unfair to allow a second-in-time drug applicant to rely on an innovator's clinical investigations while avoiding the exclusivity awarded to that same innovator, but stated that Otsuka's alternative reading would "extend the marketing exclusivity of the initial innovator drug in perpetuity" which the court explained would be "an even more absurd result." Finally, the court rejected Otsuka's contention that the FDA transgressed the Administrative Procedure Act by improperly amending or altering an unambiguous regulation in contravention of the requirements of notice and comment.

CLAIM CONSTRUCTION

Preamble Expressing the Intended Result of a Method of Treatment Is Not Limiting

Takeda Pharm. Co. Ltd. v. Actavis Labs. FL, Inc. (D. Del. June 6, 2016)

Zachary Miller

In construing a claim involving a method for treating obesity, the US District Court for the District of Delaware determined that a phrase in the preamble stating that the method of treatment had "reduced adverse effects" was not a claim limitation. *Takeda Pharm. Co. Ltd. v. Actavis Labs. FL, Inc.,* Case No. 15-451-RGA (D. Del. June 6, 2016) (Andrews, J.)

In September 2014, Takeda obtained approval from the US Food and Drug Administration (FDA) to launch Contrave®—a prescription weight loss product combining naltrexone and bupropion. When Actavis sought FDA approval for a generic version of Contrave® in 2015, Takeda filed suit asserting two method of treatment patents.

Various independent claims of the patents cover "[a] method of treating overweight or obesity having reduced adverse effects" comprising "administering" a "weight loss effective amount of a first and second compound" (*i.e.*, naltrexone and bupropion). The court held a *Markman* hearing and construed three key terms: (1) "administering"; (2) "weight loss effective amount of a first and second compound"; and (3) "having reduced adverse effects."

Administering. The parties first disagreed over the actions that would constitute "administering." Actavis' proposed construction limited administering to the physical act of delivering the compounds into the body, while Takeda wanted the construction to "include the act of a physician prescribing or otherwise directing a patient to take the drug." The court reviewed the patents' specifications and claim language and ultimately agreed with Actavis' proposed construction.

While the court noted that prior courts had come to differing conclusions regarding the construction of "administering," the court found that the patent specification and claims consistently distinguished between "administering" and a physician's

prescribing activities. Specifically, one patent stated that a prescribing physician could choose the "route of administration" and "manner of administration"—clearly delineating between a physician's acts and the ultimate act of "administering."

Weight loss effective amount. The parties next argued over whether the phrase "weight loss effective amount of a first and second compound" required each compound (*i.e.*, both naltrexone and bupropion) to be individually present in an amount that was weight loss effective (Actavis' position) or if only the combined amount had to be weight loss effective (Takeda's position). The court agreed with Takeda based on the information included in the patent specification. The court noted that the specification consistently focused on the "combination of two or more compounds" and that the specification stated that naltrexone by itself was not an effective drug for weight loss in humans. This evidence convinced the court to adopt Takeda's position.

Having reduced adverse effects. Finally, the parties disagreed over whether the phrase "having reduced adverse effects," constituted an additional limitation when it was found *only in the preamble*. First, the court noted that in general, statements of an intended result of a method claim in a preamble are typically not considered to be claim limitations. However, if the preamble recites steps or structure emphasized in the specification as important or if the patentee relies on the preamble for patentability during prosecution, the preamble should be considered limiting.

Actavis argued that the phrase should be limiting because the specification repeatedly touted embodiments with reduced adverse effects and because the prosecution history included arguments that having reduced adverse effects was an unexpected result. The court, however, agreed with Takeda. It stated that there was no reason to part from prior case law—that "having reduced adverse effects" was simply the "intended result" of the method and did not change the steps of the claim. Furthermore, the court noted that at least one independent claim (containing the same preamble language) included language relating to "having reduced adverse effects" in the body of the claim. Finally, the court found that none of the statements in the prosecution history regarding unexpected results were used to distinguish the claims at issue from the prior art—and therefore did not suggest that the preamble was limiting.

ANTITRUST

Second Circuit: No Valid Sherman Act Claim Where Citizen Petition Denied Contemporaneously with ANDA Approval

Apotex Inc. v. Acorda Therapeutics, Inc. (2d Cir. May 16, 2016)

Lisa A. Peterson

The US Court of Appeals for the Second Circuit held that a pharmaceutical manufacturer failed to state a Sherman Act Section Two claim because the court could not plausibly infer that a competitor filed a sham citizen petition when the citizen petition was denied on the same day the manufacturer's abbreviated new drug application (ANDA) received approval from the US Food and Drug Administration (FDA). *Apotex Inc. v. Acorda Therapeutics, Inc.*, N. 12-4353-cv (2d Cir., May 16 2016) (Jacobs, C.J.)

Apotex and Acorda are rival manufacturers for tizanidine (generic Zanaflex®) tablets and capsules, a drug that treats spasticity in patients with multiple sclerosis and Parkinson's Disease. Acorda acquired the rights to Zanaflex tablets and capsules in July 2004 and within a year, launched Zanaflex capsules. In 2007, Apotex filed an ANDA for tizanidine capsules in order to provide generic competition to Acorda's Zanaflex capsules. Acorda then initiated a patent infringement suit against Apotex in which a district court found Apotex's patent was invalid. Shortly thereafter, Acorda filed a citizen petition with the FDA objecting to Apotex's ANDA application because Apotex's product was allegedly not bioequivalent to Acorda's reference listed drug and included allegedly misleading or false statements on its label. Ultimately, the FDA denied Acorda's citizen petition on the same day it approved Apotex's ANDA.

Apotex brought Sherman Act Section Two claims against Acorda, claiming Acorda attempted to monopolize the market for tizanidine capsules by delaying Apotex's entry into the market. A district court found Apotex failed to show that Acorda's citizen petition was objectively baseless and granted Acorda's motion to dismiss. It reasoned that reliance on the temporal proximity of the FDA's decisions on the ANDA and citizen petition alone was insufficient to state a Sherman Act

claim in light of recent legislation directing the FDA not to delay the ANDA process because of a citizen petition, as well as narrowing the grounds on which the FDA could delay an ANDA. The court affirmed and reasoned that the recent legislation undermined past precedent which inferred that the "mere simultaneity of ANDA and citizen petition decisions is indicative of the delay of one by reason of pendency of the other." The court explained that because recent FDA guidance states it is preferable to issue a decision on an ANDA before issuing a decision on a citizen petition, the mere simultaneity of the decisions alone cannot prove that the citizen petition was an "anticompetitive weapon" and a sham. Rather, a claimant must show the citizen petition was "objectively baseless" to demonstrate that the citizen petition was an attempt to directly interfere with competition. The court further explained that it is not enough to show that the citizen petition was ultimately unsuccessful; instead, a claimant must show the arguments advanced in the competitor's petition were false, not that they simply "fail[ed] to move the FDA."

PRACTICE NOTE

Pharmaceutical manufacturers bringing antitrust claims alleging a competitor filed a sham citizen petition to delay the manufacturer's competition to the market must plead facts beyond (1) the coincidental timing of the FDA's decision regarding the ANDA and the citizen petition, and (2) the ultimately fruitless nature of the citizen petition.

FOR MORE INFORMATION

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