2015-2067

United States Court of Appeals for the Federal Circuit

ELI LILLY AND COMPANY,

Plaintiff – Appellee,

v.

TEVA PARENTERAL MEDICINES, INC., APP PHARMACEUTICALS LLC, PLIVA HRVATSKA D.O.O., TEVA PHARMACEUTICALS USA, INC., BARR LABORATORIES, INC.,

Defendants – Appellants.

Appeal from the United States District Court for the Southern District of Indiana in No. 1:10-cv-01376-TWPDKL, Judge Tonya Walton Pratt.

BRIEF OF AMICUS CURIAE BIOTECHNOLOGY INNOVATION ORGANIZATION IN SUPPORT OF PLAINTIFF-APPELLEE

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CERTIFICATE OF INTEREST

Counsel for *amicus curiae* Biotechnology Innovation Organization certifies the following:

1. The full names of every party or amicus represented by us is:

   Biotechnology Innovation Organization

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by us is:

   Not applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by us is:

   None.

4. The names of all law firms and the partners or associates that appeared for any of the parties or *amicus* now represented by us in the trial court or agency or in a prior proceeding in this case or are expected to appear in this Court are:

   Hans Sauer of Biotechnology Industry Organization;

   David S. Forman of Osha Liang LLP.

March 11, 2016

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INTEREST OF AMICUS CURIAE

The Biotechnology Innovation Organization (BIO) is a trade association representing over 1,000 companies, academic institutions, and biotechnology centers. BIO members are involved in research and development of biotechnological healthcare, agricultural, environmental, and industrial products. For the healthcare sector, the biotechnology industry has more than 370 therapeutic products currently in clinical trials to treat over 200 diseases. The majority of BIO members are small companies that have yet to bring a product to market and attain profitability.

BIO is interested in this case because its members must rely heavily on the patent system to protect their platform technologies and commercial embodiments. Enforceable patents that cannot be easily circumvented enable biotechnology companies to secure financial support to advance biotechnology products through regulatory approval to the marketplace, and to engage in the partnering and technology transfer necessary to translate basic life science discoveries into real-world solutions for disease, pollution, and hunger.

Proprietary biotechnological processes and method patents protecting them are often a biotechnology company's most valuable assets. The steps of such processes can often be practiced by different entities. BIO members have a strong interest in clear, ascertainable rules of infringement liability that

discourage parties from circumventing this liability by dividing up otherwise infringing activities. Accordingly, BIO submits this brief to assist this Court's longstanding efforts to guide the evolution of patent law in a uniform and predictable way that accommodates new emerging technologies and to guard against unforeseen consequences that might cripple reasonable, business-based expectations in the life sciences.

No counsel for any party authored this brief in whole or in part, and no one other than BIO and its members has made a monetary contribution to the preparation or submission of this brief. Plaintiff–Appellee Eli Lilly and Company has consented to filing of this brief, but Defendants–Appellants take no position on this brief. Pursuant to Fed. R. App. P. 29(b), this brief is therefore accompanied by a motion for leave to file.

ARGUMENT

I. Process Patent Claims Are Vital to Biotechnology Companies

The biotechnology industry needs rules for infringement of patented methods (also known as process patents) that are reasonable, and capable of future, orderly application to the great variety of biotechnology process patents. Process patents are extremely important in biotechnology. For example, the use of biomarkers in medical therapy inherently involves the application of biological assays in combination with treatment selection or therapy steps, involving participation of laboratory professionals, physicians, and patients. Importantly, virtually no major clinical trial is conducted today without a biomarker component. These methods allow targeted treatment of patients who are particularly likely to benefit from the drug and avoid side-effects, as well as to enable redirection of other patients to alternative therapies. Because laboratory assays and drug administration are typically performed by separate entities, however, the claims that would protect these methods would be vulnerable to circumvention under a rigid single entity rule.

Method patents also play an important role in protecting biologic drug products. Large ongoing investments are made to study new indications and improved methods of delivering such drugs long after the drug itself has been patented. In BIO's experience, major clinical trials commonly cost well over

$100 million, and have been as high as $800 million. Method patents are often the only feasible way to protect these investments.

The use and importance of method patents is not limited to the biomedical field. In agricultural and environmental biotechnology, process patents play similar major roles in the production of biofuels and bioplastics. In plant breeding and hybridization, for example, novel use of biomarkers for marker-assisted trait selection is likewise difficult to protect without process patents. The appellant's cramped interpretation of divided infringement of method claims invites circumvention of a particularly valuable subset of biotechnology patents by "dividing up" the steps of patented methods for separate practice.

II. There Is Direct Infringement of a Process Patent When Performance of All the Method Steps Are Attributable to One Actor

A defendant cannot be liable for inducing infringement of a process patent under 35 U.S.C. §271(b) if no one actor has directly infringed the process patent under §271(a). *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 134 S. Ct. 2111, 2120 (2014). In *Limelight* the Supreme Court initially held that there was no infringement under §271(a) because no single party performed all steps of a method claim. In remanding, the Supreme Court invited this Court "to revisit the §271(a) question." *Id.* at 2120. The Federal Circuit did so in *Akamai Techs., Inc. v. Limelight Networks, Inc.*, 797 F.3d 1020 (Fed. Cir. 2015) (en banc), unanimously holding that where more than one actor is involved in practicing

the steps of a claimed method, there can be infringement under §271(a) if the acts of one party are attributable to the other, such that a single entity is responsible for the infringement. An entity is responsible for another's performance of method steps (1) where that entity directs *or* controls the other's performance, or (2) where the actors form a joint enterprise. *Id*. at 1022 (emphasis added). Whether a single actor has directed the acts of a third party is a question of fact. *Id.* at 1023.

In this case, the Appellants (collectively, "Teva") and their amicus Generic Pharmaceutical Association ("GPhA") propose various theories for confining this Court's "direction or control" test to the particular pattern found in *Akamai*, in order to argue that the infringing acts of third parties (here patients) cannot be attributed to the infringing acts of others (here prescribing physicians). BIO believes that the instant case meets all requirements for "direction or control" under this Court's *Akamai* decision, and submits this brief to urge the Court to retain an infringement standard that is not unreasonably limited to the facts presented in *Akamai*.

III. The Specific Facts in the Akamai Case Do Not Create a Rule That Must Apply to All Divided Infringements

This is not a difficult case. The district court found that the facts that established direction or control in *Akamai* map well onto the facts of the instant dispute. Lilly presented sufficient evidence that physicians would condition

participation in pemetrexed treatment, and its benefit, upon performance of the folate treatment step, and would establish the manner or timing of that performance—all in accordance with both Teva's proposed label and Lilly's patent. L.Br.[1] 21-23; A27-28. Thus the *Akamai* factors are met, providing sufficient evidence to affirm the existence of "direction or control" in this case.

While the *Akamai* direction or control factors are thus sufficient to decide this case, a major error infects most of the arguments of Teva and GPhA, creating concern for the future orderly development of the law of divided infringement. Appellants take the specific evidentiary factors that proved direction or control in *Akamai*, 797 F.3d at 1023, and assume that those factors constitute the exclusive elements that must be satisfied for the infringing acts of one party to be attributed to another. They argue that Lilly has failed to prove that it "conditions participation in an activity or receipt of a benefit upon performance of a step or steps of a patented method and establishes the manner or timing of that performance." T.Br at 20-22; GPhA Br. at 8-15. Teva contends that this test requires that one infringing actor "essentially compels" the other party's infringing act. T.Br. at 22.

[1] "L.Br." refers to Brief of Plaintiff-Appellee [Eli Lilly and Company]; "T.Br." refers to Brief for Defendants-Appellants [Teva Parenteral Medicines et al.], and "GPhA Br." refers to Brief of Amicus Curiae Generic Pharmaceutical Association in Support of Defendants-Appellants.

But this court made clear in *Akamai* that "[t]oday we outline the governing legal framework for direct infringement and *address the facts presented by this case*. In the future, *other factual scenarios may arise which warrant attributing others' performance of method steps to a single actor*. Going forward, *principles of attribution are to be considered in the context of the particular facts presented*." 797 F.3d at 1023 (emphasis added). Based on the specific facts in *Akamai*, this Court found that that there was substantial evidence in that case of direction and control, because the infringer conditioned its customers' use of its content delivery network upon its customers' performance of the tagging and serving steps, and that it established the manner or timing of its customers' performance. *Id*. at 1024-25. But this was clearly a fact-based analysis of the evidence in that case, not an exclusive requirement for all future cases involving divided infringement. *Id*. at 1025. Whether a party directs or controls actions of a third party must be analyzed based on the facts of each case in question.

BIO urges the court to not limit the test of "direction or control" to the specific *Akamai* factual elements. As discussed above, Section I, a variety of method patents in the field of biotechnology have steps that are amenable to performance by more than one actor. Some of these might fit neatly into all of the *Akamai* facts. But others may not. It does not make sense to require proof, a priori, that an actor "conditions participation in an activity or receipt of a benefit upon performance of a step or steps of a patented method and establishes the

manner or timing of that performance." Of course, the Court cannot now decide such cases which are not before it. But BIO urges the Court to avoid setting precedents that would unnecessarily complicate or frustrate the analysis of divided infringement in much different factual situations.

IV. Teva's Theories Would Erect Barriers of Proof in ANDA Cases That Unreasonably Narrow the Scope of Divided Infringement

This appeal reaches this Court on a simple proposition. Teva intends to supply a competing product with directions to practice exactly what is claimed in Lilly's patent. Teva would induce downstream users - in writing - to practice every step of the patented method, yet argues that "no one" would infringe the patent. As a result of such infringement by "no one," Lilly can expect to lose 89% of its market share within one year.[2].

Teva, supported by GPhA, justifies its desired outcome by arguing that the directions it provides with its product label might not actually be followed by physicians and patients. T.Br. at 23-26; GPhA Br. at 17-18. They argue that there is no proof that physicians would enforce the directions on the drug's label as written. T.Br. at 26; GPhA Br. at 15. And, at bottom, they demand proof that even patients who would follow their physician's directions would do so because they are compelled, and not of their own free will.

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[2] See: Grabowski, Long, and Mortimer, *Recent Trends in Brand-Name and Generic Drug Competition*, J. Med. Economics, 2013, 1-8, at p. 6 (2013)(explaining that for pioneering new molecular entity drugs with annual sales exceeding $250M during the 2011-2012 period, market share had fallen to 11% at one year after generic entry).

Infringement in an ANDA case must be established by the plaintiff, just like in any other case.

> The substantive determination whether actual infringement or inducement will take place is determined by traditional patent infringement analysis, just the same as it is in other infringement suits, including those in the non-ANDA context, the only difference being that the inquiries now are hypothetical because the allegedly infringing product has not yet been marketed.

Warner Lambert v. Apotex, 316 F.3d 1348, 1365(Fed. Cir. 2003). This being an ANDA case, no actual use of the generic product has yet occurred. Thus, the ANDA "must be judged on its face for what an accused infringer seeks the FDA's approval to do," without resort to speculation. *Id.* at 1364 "The infringement case is therefore limited to an analysis of whether what the generic drug maker is requesting authorization for in the ANDA would be an act of infringement if performed." *Id.*

Teva and GPhA confuse the infringement inquiry by suggesting that patients might ignore their doctors' instructions based on the approved label and not take folate, or that doctors might treat patients with pemetrexed absent prior folate administration. T.Br. at 23-26; GPhA Br. at 17-18. At bottom, they imply that despite written instructions to the contrary, some step of the patented method might not actually be practiced at all. And that the patentee must prove that it would be. All in spite of the fact that Defendants' experts agreed with Lilly's

experts that doctors would not administer the drug without prior folate administration. L.Br. at 21-23.

But in ANDA cases the court must assume that a drug product will actually be used in the manner for which FDA approval is being sought. Even Teva confirms that the question of infringement under 35 U.S.C. 271(e) should not be resolved by reaching outside the defendant's label. T.Br. at 25. If the use of defendant's drug *according to the label* would result in the practice of all steps of the patented method, then the all-elements rule of infringement is met. In a multiple actor scenario the question then becomes not whether the actors would actually practice the steps as the label requires, but whether these actors, if they were to do so, would be in the requisite legal relationship.

As Teva and GPhA are no doubt aware, drug labels are unlikely to always contain proof of that legal relationship as explicitly as the appellants would require. The content of drug labels is highly regulated by the FDA. Drug labels are first and foremost concerned with the safe and efficacious use of the labeled drug; they contain warnings and instructions for use, product specifications, and other required safety and traceability information. They leave no room for extraneous information. In particular, they are *not* concerned with the relationships between doctors and patients, and seek neither to define nor control such relationships in legal terms. It is folly to expect all drug labels to specify

ways in which a physician is to "compel" patient compliance with her or his instructions.

Nor does it matter that some patients, unbeknownst to the physician and contrary to instructions, might not take a step that is required of them. Questions of patient compliance are too common and manifold to be regulated by the FDA.[3] Such issues cannot be addressed other than through the physician's discretion, experience, and professional standards. The ordinary standards of care will dictate how the physician "enforces" a particular condition of treatment. Sometimes a physician may require a test to ensure a patient's compliance, sometimes verbal reconfirmation may be sufficient, and often the physician may reasonably assume that rational patients will follow medical instructions on their own, without policing or threat of sanctions.

It is irrelevant that Teva's label here does not specify any level and means of coercion that a physician is to exercise over her or his patients. What matters is that Teva's label clearly tells the physician to direct the patient to premedicate with folate. The product labeling instructs physicians to initiate supplementation with oral folic acid prior to initiating pemetrexed in order to reduce the severity of potentially fatal toxicities. A11255. In a section headed *Requirement* for Premedication and Concomitant Medication to Reduce Toxicity (emphasis

[3] As will be attested by anyone who has ever been required not to eat breakfast; drink coffee, take blood thinners, etc. before a medical procedure, treatment, or test. Regulating compliance with such requirements is neither the FDA's nor a product manufacturer's job.

added) the physician is instructed "Prior to treatment with ALIMTA, initiate supplementation with oral folic acid and intramuscular vitamin B12 to reduce the severity of hematologic and gastrointestinal toxicity of ALIMTA [see Dosage and Administration (2.3)]". A11256. This instruction is repeated in the Dosage and Administration section. *Id.* Most significantly, the physician is told to "[i]nstruct patients to read the patient package insert before initiating ALIMTA. Instruct patients on the need for folic acid and vitamin B12 supplementation to reduce treatment-related hematologic and gastrointestinal toxicity . . . ." Thus, physicians are clearly told to instruct their patients to take the folic acid in the claimed manner. Furthermore, based on information in the label the physician and patient will both have strong motivation to perform their respective steps in the method to avoid unnecessary toxicity.[4]

Assuming, as we must for purposes of an infringement inquiry under 35 U.S.C. 271(e)(2), that defendant's product would be used as labeled, a doctor who uses pemetrexed would thus start the treatment by instructing the patient to begin premedication with oral folate. The label informs the doctor that failure to

[4] Even if the label did not explicitly require the physician to "instruct" or "direct" the patient, it will often be the case that such instruction or direction will necessarily occur, or at least can be inferred from the label when read against the background of ordinary medical practice. The organizing principle that structures the physician-patient relationship is the "duty to do no harm." These goals are not simply aspirational. The law assumes that physicians adhere to a certain standard of care when administering drugs. Under this standard, a physician has a duty to use reasonable care and diligence when administering drugs to protect the safety and well-being of the patient.

take folate increases the risk of serious gastrointestinal and hematologic toxicity of pemetrexed. Physicians have a responsibility to their patients to not expose them to avoidable harm. Patients, in turn, seek the benefit of treatment for the labeled indication. It is clear, then, that the label establishes premedication with oral folate as a condition of the remaining treatment steps. This constitutes sufficient proof for an ANDA infringement inquiry.

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In ANDA cases where the asserted patent claims a method of using the drug that is not explicitly on its label, ANDA applicants greatly benefit from an infringement inquiry that confines itself to the defendant's label. E.g., *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1352, 1364-65 (Fed. Cir. 2003) (no infringement where ANDA did not disclose using drug for method of asserted patent, even if defendant had knowledge that the drug would predominantly be used in infringing ways). Here, however, Teva applies for FDA approval precisely for the patented use of Lilly's drug, yet seeks to escape liability by speculating about conduct that is extraneous to its label. Sometimes, sauce for the goose is sauce for the gander. This court should not endorse an infringement analysis that limits a patentee strictly to the defendant's label to establish infringement, while allowing an accused infringer to reach for conduct outside its label when seeking to escape liability.

V. This Case Does Not Create New "Liability" For Physicians

Amicus GPhA expresses policy concerns that the district court's decision could expose physicians to new, strict liability for the conduct of their patients. GPhA Br. at 18-20. But this is not a medical liability case, nor does the district court's opinion implicate this area of tort law. It has always been the case that consumers or end-users of infringing products (including physicians) could nominally be thought of as infringers. For example, direct infringement formally already exists when a physician administers an infringing drug outside the divided infringement context, so it is difficult to see how the district court's opinion would layer on additional "liability." At any rate, in practice, health care providers are simply not held liable for patent infringement for using an infringing drug. It would be irrational for any drug manufacturer to attempt patent enforcement against end-users of a drug. There is no reward in doing so, and suing physicians for treating patients would, in effect, punish them for the societally beneficial practice of administering medicine. Any financial rewards would be overshadowed by the inevitable public backlash.

More to the point, this case—like the majority of patent cases in the pharmaceutical space—proceeds, as it must, under the provisions of 35 U.S.C. §271(e)(2), which limits the universe of possible defendants to ANDA filers, and provides no mechanism for suing physicians. The argument about the creation of infringement liability for physicians is a red herring.

CONCLUSION

It is telling that neither Teva nor GPhA in any way ground their arguments in sound policy, fairness, or common sense. No such grounds exist for their proposition. Appellant's theories do not help protect innocent actors from liability for the conduct of others; they do not protect the statutory scheme for indirect infringement against subversion by theories of direct infringement, nor do they serve any other fairness or policy concern that animates this court's jurisprudence in the areas of inducement or divided infringement. Their arguments, plain and simple, seem aimed at making it easier to knowingly and intentionally infringe valid patents, with no offsetting policy benefits. If adopted, Appellant's theory would be outcome-determinative in future cases even where the asserted patent is valid, its unauthorized practice is demonstrated, and the robust requirements for a claim of active inducement are met.

BIO respectfully urges the Court to affirm the district court for the reasons of record. But in doing so the Court should avoid narrowing its legal framework for analyzing divided infringement.

Respectfully submitted,

March 11, 2016

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Eli Lilly and Company v. Teva Parenteral Medicines, 2015-2067

CERTIFICATE OF SERVICE

I, Elissa Matias, being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

Counsel Press was retained by *Amicus Curiae,* BIOTECHNOLOGY INNOVATION ORGANIZATION to print this document. I am an employee of Counsel Press.

On **March 11, 2016**, Counsel for *Amicus Curiae* has authorized me to electronically file the foregoing **Motion for Leave to file Brief for *Amicus Curiae* Biotechnology Innovation Organization** with the Clerk of Court using the CM/ECF System, which will serve via e-mail notice of such filing to any of the following counsel registered as CM/ECF users:

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March 11, 2016

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