United States Court of Appeals for the Federal Circuit

TAKEDA PHARMACEUTICALS U.S.A., INC.,
Plaintiff-Appellant

v.

WEST-WARD PHARMACEUTICAL CORPORATION, HIKMA AMERICAS INC., HIKMA PHARMACEUTICALS PLC,
Defendants-Cross-Appellants

2015-1139, 2015-1142

Appeals from the United States District Court for the District of Delaware in No. 1:14-cv-01268-SLR, Judge Sue L. Robinson.

Decided: May 6, 2015

JEFFREY I. WEINBERGER, Munger, Tolles & Olson LLP, Los Angeles, CA, argued for plaintiff-appellant. Also represented by TED G. DANE, ELIZABETH LAUGHTON; ERIC KELVIN CHIU, AMY GREYWITT, San Francisco, CA; MARY W. BOURKE, Womble, Carlyle, Sandridge & Rice, PLLC, Wilmington, DE; TRYN T. STIMART, Tysons Corner, VA .

CHARLES B. KLEIN, Winston & Strawn LLP, Washington, DC, argued for defendants-cross appellants. Also represented by JOVIAL WONG, STEFFEN NATHANAEL JOHNSON; SAMUEL S. PARK, Chicago, IL; WILLIAM G. JAMES, II, WILLIAM M. JAY, Goodwin Procter LLP, Washington, DC.

EDWARD A. MARSHALL, Arnall Golden Gregory LLP, Atlanta, GA, for amicus curiae The American College of Rheumatology.

MELISSA ARBUS SHERRY, Latham & Watkins LLP, Washington, DC, for amicus curiae Generic Pharmaceutical Association.

Before NEWMAN, DYK, and HUGHES, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* DYK.

Dissenting opinion filed by *Circuit Judge* NEWMAN.

DYK, *Circuit Judge*.

Takeda Pharmaceuticals U.S.A., Inc. ("Takeda") appeals the order of the United States District Court for the District of Delaware denying its motion for preliminary injunction. Takeda sought to enjoin West-Ward Pharmaceutical Corporation, Hikma Americas Inc., and Hikma Pharmaceuticals PLC (collectively "Hikma") from continuing its launch of Mitigare, a colchicine product for prophylactic treatment of gout, and from launching an authorized generic version of Mitigare. We affirm.

BACKGROUND

Takeda owns several asserted patents[1] that cover several methods of administering colchicine products to treat gout. Colchicine itself, which has been used for centuries, is not covered by Takeda's patents. The '647 and '938 patents (the "acute gout patents") are directed to methods of treating acute gout flares. The '655, '648 and '722 patents (the "drug-drug-interaction (DDI) patents") are directed to methods for administering colchicine for prophylaxis of gout in patients who are concomitantly taking certain drug inhibitors known as "CYP3A4" and "P-gp" inhibitors.

The acute gout patents recite methods of treating acute gout by administering 1.2 mg of oral colchicine at the onset of the flare, followed by 0.6 mg of colchicine about one hour later.

DDI patent '655 recites administering colchicine concomitantly with clarithromycin by reducing the typical prophylactic dosage of colchicine by 75%, including a dose of 0.3 mg once a day. DDI patent '648 recites concomitant administration with ketoconazole, where the reduced daily dose of colchicine is 25% to 50% of the daily dose, including a dose of 0.3 mg once a day. DDI patent '722 recites concomitant administration with 240 ml of verapamil, where the reduced daily dose of colchicine is 50% to 75% of the daily dose.

In 2009, Mutual was the first drug manufacturer to receive approval from the Food and Drug Administration ("FDA") to market colchicine for treatment and prophylax-

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[1] The asserted patents are U.S. Patent Nos. 7,964,648 ("the '648 patent"), 7,981,938 ("the '938 patent"), 8,097,655 ("the '655 patent"), 8,440,722 ("the '722 patent"), and 7,964,647 ("the '647 patent").

is of gout flares. Takeda acquired Mutual and the approved New Drug Application ("NDA"). Takeda sells the colchicine product under the brand name Colcrys.

In 2010, Hikma sought FDA approval of a colchicine product for prophylaxis of gout flares. It submitted an NDA under § 505(b)(2) of the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act"), codified at 21 U.S.C. § 355(b)(2). On September 26, 2014, the FDA granted Hikma approval to market its Mitigare colchicine capsule.

On October 3, 2014, Hikma launched Mitigare, and Takeda filed suit against Hikma, asserting induced infringement under 35 U.S.C. § 271(b) based on Hikma's labeling of the Mitigare product. Hikma planned on launching an authorized generic version of Mitigare as early as October 10, 2014. However, the district court granted Takeda's request for a temporary restraining order ("TRO") on October 9, 2014, restraining Hikma from selling Mitigare and from launching a generic colchicine product. The district court also restrained Takeda from launching an authorized generic version of its branded Colcrys product during the TRO and required that Takeda "provide notice to Hikma at least 10 business days before the launch of any authorized generic of Colcrys." J.A. 20.

On November 4, 2014, the district court denied Takeda's motion for preliminary injunction on the grounds that Takeda did not meet its burden of showing a likelihood of success on the merits for its induced infringement claims or irreparable injury. On the issue of the likelihood of success on the merits, the district court concluded that, although Hikma failed to raise a substantial question regarding the validity of the patents, Takeda had not met its burden of showing likelihood of proving induced infringement. On the issue of irreparable harm,

the district court concluded that Takeda had not shown a causal nexus between Hikma's infringement and Takeda's alleged harm.

In the order denying a preliminary injunction, the court also ordered that, if Takeda took an immediate appeal (the next day), "the status quo [would] be maintained pending appeal" by extending the TRO, including its 10-day notice provision. J.A. 16–17.

Takeda timely appealed the denial of preliminary injunction, and Hikma cross-appealed. In its cross-appeal, Hikma argues that the extension of the TRO was based solely on its "consent," and it should not have been extended past oral argument in this appeal. After oral argument on January 9, 2015, we issued, without dissent, an order affirming the district court's denial of preliminary injunction and vacating the TRO, including its 10-day notice provision.[2] Our order mooted Hikma's cross-appeal and Takeda's argument that the 10-day notice provision in the TRO was improper. Our vacating of the order did not affect Takeda's liability under the bond. We have jurisdiction pursuant to 28 U.S.C. § 1292(c).

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[2] The order stated:

> The district court's order denying Takeda Pharmaceuticals U.S.A., Inc.'s motion for preliminary injunction is affirmed, opinion to follow.
>
> The injunction pending appeal ordered by the district court is vacated effective immediately. The consequence of vacating the injunction pending appeal is that both parties are free to immediately offer colchicine products for prophylactic use, without regard to the 10-day provision of the district court's order.

DISCUSSION

We review a denial of a preliminary injunction for abuse of discretion. *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1345 (Fed. Cir. 2008) (citing *Doran v. Salem Inn*, 422 U.S. 922, 932 (1975)). A court abuses its discretion if it "ma[kes] a clear error of judgment in weighing relevant factors or exercise[s] its discretion based upon an error of law or clearly erroneous factual findings." *Id.* (quoting *Novo Nordisk of N. Am., Inc. v. Genentech, Inc.*, 77 F.3d 1364, 1367 (Fed. Cir. 1996)).

In general, a party seeking a preliminary injunction must establish that it is likely to succeed on the merits, that it is likely to suffer irreparable harm in the absence of relief, that the balance of equities is in its favor, and that an injunction is in the public interest. *See Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1375–76 (Fed. Cir. 2009).

I

The relevant statutory provisions here are in the Hatch-Waxman Act. The Hatch-Waxman Act allows generic manufacturers to rely on certain streamlined FDA approval processes by which generic drug manufacturers can bring their products to market without submitting all of the extensive drug and clinical data ordinarily required of an NDA under 21 U.S.C. § 355(b)(1). In particular, an applicant seeking approval to market a generic version or variant of a drug may file either an Abbreviated New Drug Application ("ANDA") or a "505(b)(2) application," sometimes called a "paper NDA." *Id.* §§ 355(b)(2), (j). An ANDA allows applicants seeking approval for generic versions of existing drugs to rely on the safety and efficacy information for an approved drug listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations*, or the "Orange Book." A paper NDA allows applicants seeking approval for a new drug or a change to

an approved drug to rely on existing FDA findings of safety and effectiveness or studies not performed by the NDA applicant.

Both the ANDA and paper NDA pathways generally require applicants to submit one of several kinds of patent certifications, *see id.* §§ 355(j)(2)(A)(vii)(I)-(IV), 355(b)(2)(A)–(B), including a "Paragraph IV" certification that the relevant patents are either invalid or not infringed, which may in turn trigger patent litigation under the artificial act of infringement created by 35 U.S.C. § 271(e)(2)(A). *See* §§ 355(j)(2)(A)(vii)(IV), 355(b)(2)(A)(iv); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 675 (1990).

Here Colcrys was an FDA-approved drug, and Hikma elected to file a paper NDA pursuant to 21 U.S.C. § 355(b)(2). Hikma did not, however, file a Paragraph IV certification with respect to Takeda's patents because it relied on prior FDA findings of safety and efficacy concerning colchicine, and did not seek FDA approval for a use covered by Takeda's patents. As Takeda concedes, "[a]dministering colchicine for prophylaxis of gout flares is not covered by Takeda's asserted patents, except when it involves concomitant administration with certain other drugs." Appellant's Br. 4 n.1.

As we explained in *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003), Congress intended "that a single drug could have more than one indication and yet that [an] ANDA applicant could seek approval for less than all of those indications." *Id.* at 1360. A patent certification such as a Paragraph IV certification need not be provided "for a patent claiming a use for which the ANDA applicant is not seeking approval." *Id.* at 1361; *see* 21 U.S.C. § 355(j)(2)(A)(viii); *Caraco Pharm. Labs. v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1677 (2012); *see also* 21 U.S.C. §§ 355(b)(2)(A)(i)–(iv), (b)(2)(B) (parallel provisions

in the paper NDA process). In such a situation, a generic manufacturer may avoid infringement by proposing a label that does not claim a patented method of use, *Caraco*, 132 S. Ct. at 1676–77, ensuring that "one patented use will not foreclose marketing a generic drug for other unpatented ones," *id.* at 1682.

II

With this statutory scheme in mind, we address the question of whether Takeda showed a likelihood of success on the merits of the induced infringement claim. Such likelihood is not shown if an alleged infringer raises a substantial question regarding either infringement or validity of the asserted patents. *See Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1364 (Fed. Cir. 1997).

A

We first consider induced infringement with respect to the acute gout patents. Since Hikma did not seek FDA approval to market Mitigare for treatment of acute gout flares, Mitigare's label stated that Mitigare is "indicated for prophylaxis" and that the "safety and effectiveness of [it] for acute treatment of gout flares during prophylaxis has not been studied." J.A. 138. The label also said that "[i]f you have a gout flare while taking [Mitigare], tell your healthcare provider." J.A. 148. Takeda argued that this latter statement induced infringement because, in the case of the patient taking Mitigare for prophylaxis, the physician would likely tell the patient to use the Mitigare product to treat the acute flare. The district court concluded that the latter instruction was not sufficient to establish induced infringement. We agree.

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). "[The] sale of a lawful product by lawful means, with the knowledge that an unaffiliated, third party may infringe,

cannot, in and of itself, constitute inducement of infringement." *Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1276 n.6 (Fed. Cir. 2004) (internal quotation marks and citation omitted). The accused infringer must have "knowingly aided and abetted" direct infringement. *Warner-Lambert*, 316 F.3d at 1363 (citations omitted).

As the Supreme Court held in the analogous context of copyright infringement, there is no indirect infringement "when a defendant merely sells a commercial product suitable for some lawful use." *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 936 (2005) (citing *Water Techs. Corp. v. Calco, Ltd.*, 850 F.2d 660, 668 (Fed. Cir. 1988)). Infringement only exists where there is evidence that "goes beyond a product's characteristics or the knowledge that it may be put to infringing uses." *Id.* at 935. Inducement can be found where there is "[e]vidence of active steps taken to encourage direct infringement," which can in turn be found in "advertising an infringing use or instructing how to engage in an infringing use." *Id.* at 936 (citations and internal quotation marks omitted).[3] But such instructions need to

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[3] We have specifically approved *Grokster*'s definition in the patent context. *See Ricoh Co., Ltd. v. Quanta Computer Inc.*, 550 F.3d 1325, 1341 (Fed. Cir. 2008) (noting that "we turn to *Grokster* and its analysis of the law of active inducement," quoting *Grokster*, and stating that inducement requires evidence of promotion, active steps, or encouragement). Well before *Grokster*, we had adopted a virtually identical test. For example, in *Water Technologies* (a *patent* case cited approvingly by the Supreme Court in *Grokster* in its analysis of inducement, *see* 545 U.S. at 936), we noted that inducement requires "*actively . . . aiding and abetting* another's direct in-

evidence "intent to *encourage* infringement." *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1329 (Fed. Cir. 2009) (emphasis added). The question is not just whether instructions "describ[e] the infringing mode," *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1365 (Fed. Cir. 2012) (distinguishing *Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321 (Fed. Cir. 2010)), but whether the "instructions teach an infringing use of the device *such that* we are willing to infer from those instructions an affirmative intent to infringe the patent," *Vita-Mix*, 581 F.3d at 1329 n.2 (emphasis added). Merely "describ[ing]," *Toshiba*, 681 F.3d at 1365, an infringing mode is not the same as "recommend[ing]," *id.*, "encourag[ing]," *Grokster*, 545 U.S. at 930, or "promot[ing]," *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1365 (Fed. Cir. 2004), an infringing use, or suggesting that an infringing use "should" be performed, *see Arthrocare Corp. v. Smith & Nephew, Inc.*, 406 F.3d 1365, 1377 (Fed. Cir. 2005) (finding inducement where instruction manuals indicated product should be used in infringing manner).

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fringement." *Water Techs.*, 850 F.2d at 668 (emphasis added); *see also Warner-Lambert*, 316 F.3d at 1364 ("In the absence of any evidence that Apotex has or will *promote* or *encourage* doctors to infringe the neurodegenerative method patent, there has been raised no genuine issue of material fact [as to inducement]" (emphases added)); *Tegal Corp. v. Tokyo Electron Co.*, 248 F.3d 1376, 1378–79 (Fed. Cir. 2001) (explaining that inducement requires an "affirmative act," including that which "causes, or urges, or encourages, or aids another to infringe a patent" (citation omitted)); *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990) (inducement requires "intent to encourage another's infringement").

The principles that can be distilled from these cases are applicable in the Hatch-Waxman Act context where, as here, it is alleged that the drug label induces infringement by physicians. The label must encourage, recommend, or promote infringement. *See Grokster*, 545 U.S. at 936; *Toshiba*, 681 F.3d at 1365; *Metabolite*, 370 F.3d at 1365. The mere existence of direct infringement by physicians, while necessary to find liability for induced infringement, is not sufficient for inducement. As we stated in *Warner-Lambert* in the ANDA context, it is well-established that "mere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven." 316 F.3d at 1364 (citation omitted).

This requirement of inducing acts is particularly important in the Hatch-Waxman Act context because the statute was designed to enable the sale of drugs for non-patented uses even though this would result in some off-label infringing uses. *See Caraco*, 132 S. Ct. at 1681–82 ("Congress understood [that] a single drug may have multiple methods of use, only one or some of which a patent covers" and that the statute "contemplates that one patented use will not foreclose marketing a generic drug for other unpatented ones."); *Warner-Lambert*, 316 F.3d at 1359 (the Hatch-Waxman Act was not intended "as a sword against any competitor's ANDA seeking approval to market an off-patent drug for an approved use not covered by the patent").

Takeda concedes that mere knowledge of off-label infringing uses of Mitigare's product would not establish inducement. Similarly insufficient is Hikma's knowledge, acquired from the FDA, that colchicine is used to treat acute gout flares. The FDA has previously told healthcare providers to prescribe Colcrys for acute gout flares, and the FDA told Hikma that "it may be natural for the provider to use [Mitigare] for acute treatment." Appel-

lant's Br. 37. So too the guidelines from the American College of Rheumatology ("ACR") that recommend prescribing Colcrys for acute gout flares are irrelevant to the question of inducement. All of this, without more, is mere knowledge of infringing uses and does not establish inducement.

But Takeda argues that Mitigare's label, though indicated only for prophylaxis of gout, induces infringement by stating that "[i]f you have a gout flare while taking Mitigare, tell your healthcare provider," J.A. 148. Although this is neither an explicit nor implicit instruction to take Mitigare for acute gout treatment, Takeda argues that the instruction to "tell your healthcare provider" will "inevitably" lead to physicians who are consulted to advise patients taking Mitigare for prophylaxis to simply increase their dose of Mitigare to treat acute gout flares, and that Hikma was aware of or willfully blind to this possibility. Hikma argues that the label's statement that the "safety and effectiveness" of Mitigare "for acute treatment of gout flares during prophylaxis has not been studied" bars a finding of inducement, relying on *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1324 (Fed. Cir. 2012). We need not address whether or not lack of approval language precludes a finding of inducement.

Given the statutory scheme explained above, vague label language cannot be combined with speculation about how physicians may act to find inducement. This would seem to too easily transform that which we have held is "legally irrelevant," *Warner-Lambert*, 316 F.3d at 1364—mere knowledge of infringing uses—into induced infringement.[4]

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[4] Takeda even goes so far as to suggest that the label needs to contain a "clear statement" to show that it

But we need not decide whether evidence as to the invariable response of physicians could ever transform a vague label into active encouragement. Here, even if we do look outside the label, there is no evidence that the label would necessarily lead doctors who are consulted by patients taking Mitigare to prescribe an off-label use of it to treat acute gout flares.

First, Takeda does not dispute that there are a host of alternatives for treating gout flares. These alternatives include non-steroidal anti-inflammatory drugs such as indomethacin or naproxen and systemic and intra-articular corticosteroids. As the 2012 ACR Guidelines for Gout Management explain, "it is at the discretion of the prescribing physicians to choose the most appropriate monotherapy based on the patient's preference, prior response to pharmacologic therapy for an acute gout attack, and associated comorbidities." J.A. 387. Takeda points to no record evidence that physicians would forego these alternatives and simply increase the dose of Mitigare when it failed to work as a prophylactic. Indeed, the ACR says that because colchicine can cause various adverse side effects, "[r]heumatologists rarely use colchicine for acute gout flares but utilize colchicine frequently for chronic gout prophylaxis." J.A. 1505. Instead, non-steroidal anti-inflammatory drugs have become the "treatment choice for most acute attacks of gout." Appellee's Br. 32.

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was avoiding gout flare indication, and that Hikma needs to "believe[] Mitigare will be used for prophylaxis only." Appellant's Reply Br. 12. This turns the legal test on its head. Takeda needs to show that Hikma took affirmative steps to induce, not affirmative steps to make sure others avoid infringement.

Second, even with respect to physicians who would prescribe colchicine for the acute gout flares, there is insufficient evidence that doctors would inevitably prescribe Mitigare. Evidence that colchicine is prescribed for acute gout flares says nothing about whether Mitigare would be so prescribed. Takeda argues that, where the physician prescribes colchicine for an acute gout flare, it would be "impractical" for a patient already taking colchicine for prophylaxis not to "reach for the colchicine they have on hand" and follow Takeda's patented methods. Appellant's Reply Br. at 5. Takeda also suggested that it is "common sense" that doctors would prescribe Mitigare for an infringing use because it is already available on the shelf of the patient taking it for prophylaxis. But in *Warner-Lambert*, we already rejected the argument that it was "common knowledge" in the field that physicians routinely prescribe approved drugs for off-label uses, that information regarding the off-label prescriptions was "readily available" to the public, and that generic drugs are "commonly substitute[d]" for branded drugs. 316 F.3d at 1364; *see also ACCO Brands, Inc. v. ABA Locks Mfr. Co.*, 501 F.3d 1307, 1312–13 (Fed. Cir. 2007) (rejecting the argument that infringement can be found because a "natural and intuitive way to employ" the accused product was infringing).

Attempting to bridge this evidentiary deficit, Takeda also submitted physicians' declarations allegedly showing what physicians would do when patients consult them about acute gout flares. One of Takeda's physician declarations stated that "[*e*]*ven though* the [Mitigare] label states that the product has not been tested for use in treating gout flares, [he] believe[s] treating physicians would encourage patients to use Mitigare for this purpose" anyway because "in [his] experience, physicians will not recommend that a patient suffering a gout flare have two very similar colchicine products, i.e., Colcrys and

Mitigare, on hand." J.A. 2658–59 (emphasis added). The other declarant stated that he would "understand" that either Colcrys or Mitigare "could be used with equal effectiveness for the indications for which the other drug is approved," and that "[b]ecause the Mitigare product label does not provide a low-dose regimen for treating acute flares . . . [he] expect[s] that some doctors would consult the Colcrys product label to inform a patient using Mitigare to take colchicine according to the low-dose regimen specified in the Colcrys label." J.A. 99. Takeda contends that these declarations establish a "likelihood that *some* prescribers would practice the claimed method." Appellant's Br. 36.

Speculation or even proof that some, or even many, doctors would prescribe Mitigare for acute flares is hardly evidence of inevitability. This evidence does not show anything more than that there may be some infringing uses of Mitigare.[5]

Finally, Takeda relies heavily on *Astrazeneca LP v. Apotex, Inc.*, 633 F.3d 1042 (Fed. Cir. 2010), to argue that the label induces infringement. The asserted method claims there covered treating respiratory diseases such as asthma by administering "a nebulized dose" of budesonide, i.e., an anti-inflammatory corticosteroid

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[5] One declaration also stated that, "for a patient suffering a new or recurring acute gout attack, the patient will reach for his colchicine and follow the Colcrys low-dose regimen." J.A. 2659. This evidence does not suggest physicians would prescribe Mitigare in accordance with Colcrys' product label when consulted by patients. In fact, it seems to indicate something that undermines Takeda's argument: that a physician believes that patients will simply *ignore* Mitigare's label instructing them to consult their physician and use the drug off-label *themselves*.

suspended in a liquid to be inhaled, at a frequency of "not more than once per day." *Id.* at 1048. An accused infringer's label for a generic version of such an asthma inhaler instructed patients to take the drug "twice daily in divided doses" for a total daily dose of 0.5 mg, and that patients should "downward-titrate to the lowest effective dose." *Id.* at 1057. Because the label stated that the lowest available dose was a 0.25 mg vial, titrating down required going down from taking 0.25 mg twice a day to taking it once a day. *Id.* Thus the patient did not have to consult anything outside of the label to infringe. The instruction would "necessarily lead" to infringement. *Id.* This, we explained, was enough for "active steps" taken to "encourage" direct infringement. *Id.* at 1059. Here, in contrast, Takeda asks us to look outside the label to understand the alleged implicit encouragement in the label, even while it admits that evidence of mere knowledge of infringing uses is not sufficient.

The district court correctly concluded that Takeda did not establish a probability of success on the issue of infringement.

B

Takeda's arguments with respect to the DDI patents are similarly insufficient to support a finding of inducement. The Mitigare label warns patients that co-administration of colchicine and certain inhibitors "have been reported to lead to colchicine toxicity," that drug-drug interactions must thus "be considered prior to and during therapy," and that concomitant use "should be avoided if possible." J.A. 137. The label also warns that if co-administration "is necessary, the dose of Mitigare should be reduced and the patient should be monitored carefully for colchicine toxicity." *Id.* At one point the label also suggests that if co-administration is necessary, "the dose . . . should be adjusted by either reducing the daily

dose or reducing the dose frequency." J.A. 140. Takeda argues that this language constitutes inducement because a healthcare provider will have to determine whether co-administration is "necessary," and the physician would then follow the patented methods. Takeda submitted declarations in which a physician hypothesized that he would "typically" follow Takeda's patented methods if it was necessary to co-administer colchicine and medications "such as" the relevant inhibitors. J.A. 100.

Noting that this label language failed to recommend or suggest to physicians that the patented DDI methods should be followed, the district court found that, in any case, there was insufficient evidence "that any healthcare provider has actually practiced the methods of the DDI patents," J.A. 13. The district court concluded that Takeda did not even meet its burden to show likelihood of direct infringement, which is a prerequisite for indirect infringement. *See Ricoh*, 550 F.3d at 1341.

With respect to the '655 and '648 patents requiring a 0.3 mg dose of colchicine, the district court found that Mitigare would not likely be used to directly infringe because it comes in 0.6 mg capsules that cannot feasibly be split to reach a 0.3 mg dose of colchicine per day. Takeda argues that the capsules can be taken every other day to reach an average of 0.3 mg per day, citing in particular the language in Mitigare's label that warned patients to "either reduc[e] the daily dose or reduc[e] the dose frequency" if concomitant administration is necessary. But the district court found that, given that colchicine has a "narrow therapeutic index" whereby the margin between an effective dose and a toxic dose is narrow, this possibility was not likely. In any case, as Hikma argues, given that Mitigare's label recites a 0.6 mg "once or twice daily" recommendation and a "maximum dose" recommendation, J.A. 137, it is natural to read "reducing the dose frequency" as just instructing reducing

0.6 mg from twice daily to once daily and not to achieve the 0.3 mg dose by administering 0.6 mg every other day. The district court's findings on this issue were not clearly erroneous.

With respect to the '722 patent, which requires 0.6 mg of colchicine concomitantly administered with 240 ml of verapamil, the district court found that Takeda cited insufficient evidence this method would actually be practiced. While Takeda points out that it submitted evidence that 240 ml was the "usual" dose of verapamil, we see no clear error in the district court's finding that this was insufficient, especially since the issue is whether the *concomitant* administration occurs, and Hikma's physician experts declared that they try to and can easily avoid concomitant administration of the drugs.[6] Since there was insufficient proof of direct infringement here, we need not reach the question of whether there was evidence of inducement.

CONCLUSION

We conclude that the district court did not abuse its discretion in denying a preliminary injunction on the ground that Takeda had failed to meet its burden to show a likelihood of success on the merits. Because of our disposition, we need not reach Takeda's other arguments. The main appeal is:

AFFIRMED

The cross-appeal is:

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[6] The fact that one doctor said that he has prescribed colchicine concomitantly with the inhibitors is not evidence that other doctors would do the same, nor is it evidence of direct infringement since he did not speak of using Mitigare.

DISMISSED AS MOOT

COSTS

Costs to Hikma.

United States Court of Appeals for the Federal Circuit

TAKEDA PHARMACEUTICALS U.S.A., INC.,
Plaintiff-Appellant

v.

WEST-WARD PHARMACEUTICAL CORPORATION, HIKMA AMERICAS INC., HIKMA PHARMACEUTICALS PLC,
Defendants-Cross-Appellants

2015-1139, 2015-1142

Appeals from the United States District Court for the District of Delaware in No. 1:14-cv-01268-SLR, Judge Sue L. Robinson.

NEWMAN, *Circuit Judge*, dissenting.

This is not a simple question of the legal status of patented uses of unpatented drugs. This is a legal policy issue, for the patent law implements a complex balance between the incentive to develop new medicinal treatments in the public interest, while facilitating competition after patent expiration.

The product colchicine has been used to treat gout for centuries, but was known to have highly toxic side effects. Takeda discovered and developed modes of treatment at reduced toxicity. Takeda took these methods and products through clinical trials and FDA approval, and ob-

tained patents on the treatment methods. My colleagues hold that none of these patents is enforceable against Hikma, a new provider of colchicine.

It is agreed that Hikma is not a direct infringer of the Takeda patents, and my colleagues hold that Hikma does not induce infringement because the official Hikma "label" does not contain directions to use colchicine in accordance with the Takeda patented uses. Takeda argued that it suffices that the Hikma label directs patients to tell a health care provider if the affliction of acute gout flares arises, because the health care provider will prescribe the Takeda method of use. My colleagues hold that such circumstance cannot produce induced infringement.

In my view, these events do not produce a simple, bright line rule of law. In this preliminary injunction proceeding, the parties produced conflicting evidence as to the prevalence of gout flares and the likelihood that a doctor would prescribe the patented Takeda treatments. Precedent is also conflicting if generalized to all circumstances. In *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1364 (Fed, Cir. 2012), this court held that "[t]he existence of a substantial non-infringing use does not preclude a finding of inducement." But in *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1366 (Fed. Cir 2002) this court said that "[w]here a product has substantial noninfringing uses, intent to induce infringement cannot be inferred even when [the accused infringer] has actual knowledge that some users of its product may be infringing the patent."

The panel majority today adopts a rule that inducement cannot be found, whatever the facts of the particular medicament and use. That is seriously flawed, for the variety of medicinal situations is unlimited. In turn, the public interest in new uses, new methods, and new combination treatments is disserved by a rule that is a disin-

centive to the development of new uses of unpatented medicinal products.

Thus I dissent from the court's ruling that the provider of a known drug product, with knowledge that it is likely to be used in direct infringement, can never be liable for induced infringement. These are fact-specific circumstances, and are not amenable to final disposition at a preliminary injunction hearing. The question requires trial on the facts of this case.

DISCUSSION

The panel majority presents an incomplete picture of the facts and the law and ignores the public interest in the development of improved methods of treatment.

Although colchicine is a known gout treatment, Takeda, through its predecessor Mutual, developed new treatment protocols for acute gout flares, conducted clinical trials, including treatment for patients concomitantly taking other drugs, and secured FDA approval for safety and efficacy of specified dosages and combinations and schedule of administration. This information is included on the FDA-approved Takeda label, and omitted from the Hikma label.

Hikma provides colchicine capsules in the same 0.6 mg dosage as the Takeda approved product, but the FDA permitted Hikma to omit from its label the combinations and acute flare treatment method patented by Takeda. Instead, the Hikma label instructs users that if acute gout flares arise, "tell your healthcare provider."[1]

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[1] The FDA initially objected to this omission from the Hikma label, stating that "If Mitigare is being used for prophylaxis, it may be natural for the provider to use it for acute treatment as well." Hikma then added to its label that Mitigare was not "studied" for "safety and

Takeda argues that the Hikma label statement is an inducement to infringe, providing testimony from physicians that they would tell the patient to use the Takeda protocol. Hikma provided contrary testimony. My colleagues on this panel hold that it is "not sufficient for inducement" that physicians and patients would directly infringe the Takeda patents. Maj. Op. at 11. To the contrary, it is highly relevant, for this situation does not lend itself to a rigid, all-purpose rule of law. This should be a fact-dependent, case-by-case determination based on evidence of likelihood and intent for the particular unpatented drug and patented new use.

The panel majority goes too far, and states a general rule that provides easy avoidance of patents on new uses and improvements. The Hatch-Waxman Act is intended to encourage drug research and development, not to provide a disincentive by negating enforcement of improvement patents by the simple expedient of omitting the improvement from the label. With the removal of the patent incentive for improvements, the loser is the afflicted public.

The panel majority is incorrect in stating that "in the Hatch-Waxman Act context . . . . [t]he label must encourage, recommend, or promote infringement." Maj. Op. at 11 (citing *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 936 (2005). The FDA label is not a vehicle of promotion of any use; it is a record of approved safety and efficacy of the product as used in accordance with the label. Nor does the FDA "aid and abet" infringement by including approved uses on the label. *Grokster* is a copyright case, and although there is common law commonality in the word "inducement," questions of intent and scienter are as fact-specific in the

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effectiveness" of treatment of acute gout flares. On this statement, the FDA withdrew its objection.

copyright field as in connection with patents. An over-simplified analogy between copyright and patent causes does not aid understanding of these complex issues.

The panel majority also appears to misunderstand the Hatch-Waxman Act. The majority says "the statute was designed to enable the sale of drugs for non-patented uses even though this would result in some off-label infringing uses," Maj. Op. at 11, citing purported authority in *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1681-82 (2012); *Warner-Lambert*, 316 F.3d at 1359. That is a misreading of statute and precedent. The Hatch-Waxman Act is not designed to enable off-label uses, whether or not they are infringing.

The cited cases do not hold otherwise. To the contrary, *Warner-Lambert* states that "'[I]f there are indications which are claimed by any use patent and for which the [ANDA] applicant *is not seeking approval*, then an ANDA must state that the applicant is not seeking approval for those indications which are claimed by such use patent.'" 316 F.3d at 1359 (quoting House Report No. 98-857).

Takeda argues that the Hikma label, which mentions acute gout flares but advises afflicted persons to see a physician instead of reciting the FDA-approved protocol, suffices to induce infringement. Unlike the facts of *Warner-Lambert*, Takeda is not "asserting patents on unapproved uses," 316 F.3d at 1359. It is infringement of the approved patented uses that Takeda states is induced by instructing the patient to tell a doctor in the event of acute flares. Takeda offered evidence that the physician is likely to prescribe the Takeda protocol and dosage for treatment of acute flares. Resolution of the question of inducement depends on the facts of the case. However, the panel majority rejects even the need for such resolution, stating that "we need not decide whether evidence as to the invariable response of physicians could ever trans-

form a vague label into active encouragement." Maj. Op. 13. To the contrary: that is the issue of this case.

The trier of fact must have the opportunity to consider the evidence of how particular uses are made known and implemented for the Hikma product. The panel majority misstates my argument, for I do not propose that liability for inducement is automatic. Here, Hikma instructs that if acute flares arise, "tell your healthcare provider"; and Takeda presented evidence that the doctor is likely to prescribe the Takeda protocol, for that protocol is approved by the FDA and is known to physicians who treat gout. The panel majority errs in discarding all this as irrelevant, for the knowledge and extent and likelihood of infringement are highly relevant to whether infringement is deemed induced.

These aspects warrant full development of fact and law, and thoughtful application to this case.