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Drug Label, Method-of-Use Patents and Infringement by Inducement



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When the Food and Drug Administration approves a new drug, it also approves a package insert of the drug, *i.e.*, the drug label. A drug label details various aspects regarding the drug, including the approved indication and usage, dosage and administration, dosage forms and strengths, contraindications, warnings and precautions and adverse reactions. Therefore, a drug label provides helpful and sometimes critical information for doctors and patients alike.

A pharmaceutical company marketing a generic product generally only supplies the product with a package insert. Rarely does the company perform a step typically recited in a method-of-use patent—*e.g.*, ''treating.'' Therefore, to establish patent infringement, a patent holder must demonstrate that the company induced another to perform the claimed method. Inducement occurs when a party ''causes, urges, encourages, or aids'' a direct infringement by another party.[1] Additionally, the patentee must demonstrate that the company knowingly induced infringement and had specific intent to encourage the third party to infringe the patent,[2] although a belief by the company that the patent is invalid is not a defense to induced infringement.[3]

A package insert associated with a generic product evidences the product's ''intended'' use. However, when a brand drug has multiple indications, a company seeking to market a generic product can carve out certain indications from its label and file a section viii statement against the method-of-use patent(s) covering the carved out indications.[4]

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[1] *Tegal Corp. v. Tokyo Electron Co., Ltd.*, 248 F.3d 1376 (Fed. Cir. 2001).

[2] *See Warner–Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003).

[3] *Commil USA LLC v. Cisco Systems, Inc.* (2015), slip op., at 8, 11-13.

[4] When a brand drug has multiple indications but a generic company only seeks approval on one of them, the company can use a section viii statement to eliminate certain indications from its label under 21 U.S.C. § 355(j)(2)(A)(viii).

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This article provides an overview of case law relevant to inducement and method-of-use patents in the pharmaceutical arena.

I. Drug Label and Infringement by Inducement

A. Method-of-Approved-Use Patents

In many cases it takes more than 10 years to bring a new pharmaceutical product to market. A company marketing a new drug relies on not only compound patents but also method-of-use patents to maintain market exclusivity and recoup its investment. New uses for an existing compound are often discovered, leading to additional patent filings and FDA approval for new indications. For example, Warner-Lambert's drug—gabapentin—was discovered in the late 1970s and approved by the FDA for treating epilepsy in 1993.[5] Warner-Lambert obtained a patent for treating epilepsy with gabapentin. Gabapentin was later found to be useful for treating neurodegenerative diseases, which was also patented by Warner-Lambert. However, treating neurodegenerative diseases with gabapentin was never approved by the FDA.

Apotex filed an abbreviated new drug application (ANDA) seeking approval to market generic gabapentin for treating epilepsy upon the expiration of Warner-Lambert's ''epilepsy patent.'' The Federal Circuit held that Apotex's ANDA filing was not an act of infringement because the use for which Apotex sought approval was not covered by an existing patent and the patented use, *i.e.*, treatment of neurodegenerative diseases, was not approved by the FDA.[6] Because ''mere knowledge of possible infringement by others does not amount to inducement,'' Apotex was deemed not liable for inducing infringement even though doctors could prescribe its product ''off label'' for treating neurodegenerative diseases.[7]

The Federal Circuit's decision in *Warner-Lambert* confirmed that ''carving out'' a patented second approved indication by seeking FDA approval of an ANDA solely for a non-patented first approved indication is a viable strategy for avoiding liability for inducing infringement regardless of how doctors are actually prescribing the drug in practice.

B. Method of Pharmacologic Action in the Label, but Not in the Indications and Usage Section

In *Bayer v. Lupin*, the defendants filed an ANDA seeking approval to market a generic version of Yasmin for the FDA-approved use, oral contraception.[8] The patent at issue was directed to achieving three effects simultaneously: a contraceptive effect, an anti-androgenic effect, and an anti-aldosterone effect.[9] According to the Federal Circuit, the latter two effects were not uses approved by the FDA and therefore the ANDA filers could not be liable for inducing infringement.[10] Unlike in *Warner-Lambert*, Bayer did include the two effects in the label, albeit in the ''Clinical Pharmacology'' section and not in the ''Indication and Usage'' section.[11] The Federal Circuit held that there was no evidence that the FDA had deemed the patented use of achieving the three effects simultaneously safe and effective, as an FDA approval would require.[12]

The parties agreed that the defendants could only infringe the patent at issue if the ANDAs sought approval to market their generic products for the three simultaneous effects.[13] Because the parties limited the question before the Federal Circuit to whether the FDA had approved the use of the drug to achieve the combination of the three effects, the court did not address the question whether other sections of a drug label can be evidence of intent to induce infringement. However, the Federal Circuit in *Bayer* explicitly said that ''the point is that the label, taken in its entirety, fails to recommend or suggest to a physician that Yasmin is safe and effective for inducing the claimed combination of effects in patients in need thereof.''[14] Therefore, the Federal Circuit left open the possibility that based on the facts, sections other than the ''Indications and Usage'' may be evidence of a generic pharmaceutical company's intent to induce infringement. Subsequent to the Federal Circuit's decision in *Bayer*, district judges have in fact looked to other sections of a generic pharmaceutical company's product label, including the ''Dosage and Administration'' section, when assessing inducement.

C. Patent Claims to Dosage Amounts and Formulations

1. Takeda Pharma. U.S.A. v. Hikma Am., Inc.

In *Takeda*, the Federal Circuit recently denied a motion for preliminary injunction and held that a brand pharmaceutical company failed to meet its burden of showing likelihood of proving induced infringement.[15] Takeda's patents at issue recite methods of treating acute gout by administering 1.2 mg of a drug at the onset of the flare and 0.6 mg about one hour later.[16] The generic company, Hikma, filed an ANDA seeking approval for prophylaxis of gout flares, a use acknowledged as not covered by the asserted patents.[17] However, Hikma's label stated that the safety and effectiveness of the generic drug ''for acute treatment of gout flares during prophylaxis has not been studied'' and asked patients with a gout flare to consult their physicians.[18] Takeda argued that ''the latter statement induced infringement because the physician would likely tell the patient to use the generic drug to treat the acute flare.''[19]

The Federal Circuit stated that ''vague label language cannot be combined with speculation about how physi-

[5] *See Warner-Lambert*, 316 F.3d at 1351-52.
[6] *Id.* at 1354-55.
[7] *Id.* at 1364.
[8] *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1319 (Fed. Cir. 2012)
[9] *Id.* at 1319-20.
[10] *Id.* at 1326.
[11] *Id.* at 1322.
[12] *Id.* at 1322-24.
[13] *Id.* at 1320-21.
[14] *Id.* at 1324.
[15] *Takeda Pharma. U.S.A. v. Hikma Am. Inc.*, No. 2015-1139, 2015-1142 (Fed. Cir. May 6, 2015).
[16] *Id.* at 3.
[17] *Id.* at 7.
[18] *Id.* at 8.
[19] *Id.*

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cians may act to find inducement.''[20] Takeda attempted to rely on a similar case involving a motion for preliminary injunction, *AstraZeneca LP v. Apotex, Inc.*, where the court found that the instruction in the label would ''necessarily lead'' to infringement.[21] In *AstraZeneca*, the claims were directed to treating respiratory diseases by administering a drug ''not more than once per day,'' while AstraZeneca's label indicated that ''the drug may be administered once or twice daily.''[22] Apotex's label also warns that the patient should titrate down to the lowest effective dose to avoid any adverse effects.[23] Apotex's ANDA sought FDA approval for twice-daily use, and its label instructed patients to take the drug ''twice daily in divided doses'' for a total daily dose of 0.5 mg, and the patients should ''downward-titrate to the lowest effective dose.''[24] Because the generic drug was only available in two strengths: 0.25 mg and 0.5 mg, the court reasoned that titrating down would necessarily require 0.25 mg once a day.[25] The Federal Circuit held that AstraZeneca would likely prove induced infringement at trial and affirmed the district court's decision granting preliminary injunction.[26]

There is apparent conflict between *Takeda* and *AstraZeneca* regarding whether a generic drug's product label would necessarily instruct a third party to perform certain infringing activity.

2. United Therapeutics Corp. v. Sandoz, Inc.

United Therapeutics' Remodulin (treprostinil sodium) was approved for treating pulmonary arterial hypertension.[27] An earlier FDA-approved label required that before intravenous administration Remodulin ''must be diluted with either Sterile Water for Injection or 0.9% Sodium Chloride for Injection.''[28] United Therapeutics later discovered that Remodulin diluted with Flolan Sterile Diluent effectively reduced bloodstream infection, a problem experienced by intravenous users.[29] Subsequently, United Therapeutics obtained two patents directed to methods of killing bacteria in a pharmaceutical preparation by diluting the active agent with a high pH glycine buffer, such as Flolan Sterile Diluent.[30] The FDA also approved a revised label requiring diluting Remodulin with sterile water, saline or Flolan Sterile Diluent.[31]

Sandoz filed an ANDA together with a section viii statement carving all reference to using Flolan Sterile Diluent out of the proposed label for its treprostinil product.[32] Sandoz's proposed label provided instructions to dilute treprostinil with sterile water or saline for intravenous administration, which would not infringe the method patents at issue.[33]

The court found that Sandoz's label did not contain any explicit instruction to use the Flolan diluent or some other high pH glycine buffer.[34] The court also found that the warnings in Sandoz's label regarding the bacteria infection did not amount to an implicit instruction.[35] Rather, Sandoz's label provided not only the warnings regarding a potential risk, but also explicit instructions to reduce the risk using noninfringing methods. The court therefore concluded the language in the label did not support a specific intent to infringe the patent.

The outcome of this case might have been different if United Therapeutics had revised its label in view of the method patents at issue. United Therapeutics' label could have required the use of Flolan Sterile Diluent for intravenous administration because of the higher risk of bloodstream infection associated with the use of sterile water or saline. Such a revised label might prevent Sandoz from carving out the use of infringing methods in its proposed label.

3. Braintree Labs., Inc. v. Novel Labs., Inc.

Braintree is the approval holder of Suprep, a kit that helps prepare patients for colonoscopies. Novel filed an ANDA seeking to market a generic copy of Suprep. Certain patent claims at issue require an oral solution of from about 100 mL to about 500 mL.[36] Novel's ANDA instructed ''administration of two bottle of [oral solution]'' with each bottle having 473 mL. So, the total volume of the dose in Novel's ANDA is 946 mL.[37]

The Federal Circuit found that one bottle (half dose) of Novel's product fell within the claimed range of 100-500 mL, but remanded the case for claim construction of other claim terms.[38] Judge Timothy B. Dyk disagreed with the majority and contended that ''one bottle'' of 473 mL was not the dose approved by the FDA.[39] According to Judge Dyk, Novel's ANDA seeking approval for the use of 946 mL solution cannot induce infringement of the method patent under § 271(e)(2)(A).[40]

Judge Dyk, however, might have failed to consider the label in its entirety. The ''Dosage and Administration'' section of the label instructed patients to drink one bottle in the evening before colonoscopy and the second bottle next morning. Hence, the split dose regimen in the label would support that the FDA approved the use of 473 mL solution, *i.e.*, the patented use, and also help demonstrate that Novel's label would instruct patients to infringe the method-of-use patent.

D. Patent Claims Reciting Steps of Administration

1. IGI Labs., Inc. v. Mallinckrodt LLC

The FDA approved Mallinckdrodt's diclofenac solution (Pennsaid) for treating signs and symptoms of os-

[20] *Id.* at 12.
[21] *Id.* 15-16.
[22] *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1047-48 (Fed. Cir. 2010).
[23] *Id.* at 1048.
[24] *Id.* at 1057.
[25] *Id.*
[26] *Id.* at 1061 and 1065.
[27] *United Therapeutics Corp. v. Sandoz, Inc.*, 12-CV-01617, 2014 BL 451956, at *2 (D.N.J. Aug. 29, 2014).
[28] *Id.* at *4.
[29] *Id.* at * 5-6.
[30] *Id.* at *7-8. The claims encompass the use of Flolan Sterile Diluent. *See id.* at *4, n 7.
[31] *Id.* at *4. The statement appears in the ''Dosage and Administration'' section of the Remodulin label.
[32] *Id.* at *8-9.
[33] *Id.*
[34] *Id.* at *18.
[35] *Id.* at *21.
[36] *Braintree Labs., Inc. v. Novel Labs., Inc.*, 749 F.3d 1349, 1353 and 1362 (Fed. Cir. 2014).
[37] *Id.* at 1361-62.
[38] *Id.* at 1354-55 and 1360.
[39] *Id.* at 1361-62.
[40] *Id.* at 1363.

teoarthritis of the knee(s).[41] IGI filed an ANDA seeking approval of a generic version of Pennsaid. The use of the diclofenac solution for topical treatment of osteoarthritis of the knee in patients was known, but Mallinckrodt obtained new method-of-use patents based on its clinical trial results.[42] The patents recite a method for ''treating osteoarthritis of the knee via applying the diclofenac, waiting for it to dry, and applying either a second medication, sunscreen, or insect repellent.''[43]

In the ''Dosage and Administration'' section, the drug label instructed the patients to ''[w]ait until the treated area is dry before applying sunscreen, insect repell[e]nt, lotion, moisturizer, cosmetics, or other topical medication.''[44] The court distinguished *Bayer*, and denied IGI's motion to dismiss Mallinckdrodt's counterclaims for induced infringement, finding it inappropriate to decide at the motion-to-dismiss stage whether the patents covered the FDA-approved use of diclofenac.[45]

One could argue that the FDA did not approve every instruction included in the ''Dosage and Administration'' section here as a safe and effective use of the drug. The court in fact stated in a footnote that ''[i]t would seem odd for the FDA to have to approve as a separate use the application of sunscreen or insect repellent on top of a medication.''[46] The only discussions regarding other topical medicines in the label are the warnings for patients not to apply other topical medicines until the knee is completely dry.

Therefore, if strictly following *Bayer*, the court should probably find that the patented use is not the FDA-approved use of Pennsaid and dismiss the counterclaims. Furthermore, IGI could have strengthened its case of noninfringement if it could carve out from its proposed label all references to application of a second medication, sunscreen or insect repellent.

2. ICN Pharm., Inc. v. Geneva Pharm. Tech. Corp.

Ribavirin is indicated in combination with interferon alpha for treating hepatitis C. Defendants filed an ANDA seeking approval to market generic ribavirin. One patent at issue was directed to a method for treating a disease responsive to ribavirin, comprising the following steps: (1) recognizing progression of the disease as being mediated by Th1 lymphocytes; (2) recognizing ribavirin as being effective to promote a Th1 response and suppress a Th2 response in a certain dosage range; and (3) administering ribavirin to a patient having the disease within the dosage range.[47] The court held that the defendants would not be liable for inducing infringement because the proposed label did not mention any steps of recognizing a disease and recognizing a dosage range of ribavirin.[48]

One lesson from this case is that a label and relevant method-of-use claims must be drafted in view of each other. To show the claimed methods are the FDA-approved use, it is important that the method-of-use claims should recite key terms/elements in the ''Indication and Usage'' section of the label. For example, independent claims of the patents in this case do not even recite limitations of hepatitis C and interferon alpha, although dependent claims do.[49] Conversely, the label should also contain key terms/steps of the method claims, which is not the case here either.

Another potential issue not addressed by the court is that the method claims recite a series of steps that may or may not be performed by a single party. This involves the so called ''divided infringement'' issue discussed in the next section.

II. Method-of-Use Patents and Divided Infringement

The issue of divided infringement arises when separate entities each perform separate steps of a method claim. In *Limelight Networks, Inc. v. Akamai Technologies, Inc.*, the defendant carried out some steps claimed in the method patent at issue, while its customers performed the remaining step.[50] The Federal Circuit held *en banc* that the defendant could be found liable for inducing infringement under § 271(b) even if no one committed direct infringement.[51] The Supreme Court reversed and held that there was no direct infringement if ''performance of all the claimed steps cannot be attributed to a single person.'' Thus, the defendant cannot be liable for inducing infringement where no direct infringement has occurred.[52] On remand, the Federal Circuit heard the case *en banc* again and expanded the scope of direct infringement under Section 271(a) in situations where all the steps of a claimed method are not performed by the accused party.[53] The Federal Circuit concluded that ''[s]ection 271(a) is not limited solely to principal-agent relationships, contractual arrangements, and joint enterprise'' and that the standard is ''whether all method steps can be attributed to a single entity.''[54] Applying this standard to the facts of the case, the court held that there was sufficient evidence to support the jury's finding of direct infringement.[55]

In the context of pharmaceutical patents, some method-of-use claims can be construed as including some steps being performed by a doctor (diagnosis) and others by a patient (administering). For example, in the *ICN v. Geneva* case, the defendants could argue that a doctor will perform the steps of recognizing a disease and recognizing a dosage range of ribavirin and a patient will perform the administration step. Therefore, under the Supreme Court's *Limelight v. Akamai* decision, there is no direct infringement by one actor and the defendants could avoid the liability for inducing in-

[41] *IGI Labs., Inc. v. Mallinckrodt LLC*, CV 13-2044-RGA, 2014 BL 111483, at *1 (D. Del. Apr. 22, 2014).
[42] *See* the file history of U.S. Patent No. 8217078.
[43] *IGI Labs.*, 2014 BL 111483, at *2
[44] *Id.* at *2.
[45] *Id.* at *2-3.
[46] *Id.* at 2, foot note 3.
[47] *ICN Pharm., Inc. v. Geneva Pharm. Tech. Corp.*, 272 F. Supp. 2d 1028, 1041 (C.D. Cal. 2003), *appeal dismissed*, 101 Fed. Appx. 335 (Fed. Cir. 2004).
[48] 272 F. Supp. 2d at 1049.
[49] *Id.* at 1041.
[50] *Akamai II*, 134 S. Ct. at 2115.
[51] *Id.* at 2116-17 (citing *Akamai Technologies, Inc. v. Limelight Networks, Inc.*, 692 F.3d 1301, 1319 (Fed. Cir. 2012) (''*Akamai I*'')).
[52] *Id.* at 2120.
[53] *Akamai Technologies, Inc. v. Limelight Networks, Inc.*, No. 2009-1372, slip op. at 5. (Fed. Cir. Aug. 13, 2015) (''*Akamai III*''),
[54] *Id.* at 6.
[55] *Id.* at 9.

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fringement even if their proposed labels instructed doctors and patients together to perform the infringing methods.

III. Conclusions

A drug label not only provides useful information for doctors and patients alike, but also could play an important role in patent litigation, particularly that involves infringement by inducement claims. A generic drug's label must be closely analyzed to determine whether it includes instructions to carry out the steps recited in relevant method-of-use patent claims. Additionally, when a method-of-use claim recites multiple steps, an analysis should be conducted to determine whether the claims are amenable to a divided infringement defense.