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Skinny Labels and the Line Between Mere Information and Inducement to Infringe in ANDA Litigation



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A drug whose original patent protection for any and all uses (i.e., composition of matter protection) has expired often remains protected years afterwards by patent(s) covering later-discovered uses such as methods of dosing, administering, or manufacturing the drug, or methods of treating particular indications or subsets of patients. Such patents can be significant obstacles to competitors seeking to market a generic version of the drug. However, when there are Food and Drug Administration-approved uses of the drug that are *not* covered by patents, the practice of ''skinny labeling'' allows generic drug manufacturers to obtain FDA approval to market the generic drug for such uses. Skinny labels ''carve around'' the patented drug uses by avoiding any statement that the generic drug is approved for uses covered by the corresponding branded drug's patents that are listed in the Approved Drug Products With Therapeutic Equivalence Evaluations (commonly known as the ''Orange Book''). This allows the generic manufacturer to avoid direct infringement and thereby encourages entry of generic competition into the marketplace.

However, as a practical matter, physicians often prescribe skinny labeled generic drugs for patented uses because generics are often both cheaper and indistinguishable from the branded drugs. Courts therefore recognize that skinny labels can induce infringement of method claims relating to the branded drug. In part because drug labels must describe the drug in great detail and their contents are highly regulated by the FDA, the wording of drug labels receives intense scrutiny and occupies a central place in litigation under the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act).

An understanding of how courts read drug labels for evidence of intent to induce infringement will enable branded pharmaceutical companies to craft method-of-treatment claims to maximize potential for Orange Book listing and infringement. It will also enable generic manufacturers to make informed, strategic decisions in situations where the *FDA* might allow a skinny label but a *court* nonetheless would be likely to find active intent to induce infringement in the proposed label language. In particular, patent holders should pursue claim language that mirrors the drug label as closely as possible because generic competitors are typically required by the FDA to adopt the same or nearly identical language in view of safety and efficacy requirements. Even method-of-treatment claims of extraordinarily narrow scope—reciting specific dosage amounts or frequencies, for example—can be insurmountable ob-

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stacles to generic manufacturers where the claim limitations closely correspond with language that happens to be critical to the **safety or efficacy** of the drug, which are the touchstones of FDA approval. As for generic manufacturers, they should be wary of method-of-treatment patents that cover aspects of the treatment regimen that must be included in the skinny label for safety or efficacy reasons. For example, skinny label directions to titrate doses upward or downward (to find the optimal individual patient regimen) pose a particularly high risk of inducing infringement even if the skinny label omits stating the patented optimal dose ranges. Courts have also inferred intent to induce based on language directing physicians to condition receiving the drug on the patient having taken another medication beforehand. On the other hand, courts generally decline to infer intent to induce from label language that merely provides information or safety warnings to physicians—even if physicians would routinely follow the warnings and thereby infringe a patent.

The complex and fact-specific legal landscape surrounding method-of-treatment patents in Abbreviated New Drug Application (''ANDA'') litigation is critically important to the dual public policy goals of pharmaceutical innovation and cost-effective generic competition. Recent case law reveals a tension between avoiding unfair *de facto* patent term extensions to branded pharmaceutical companies on the one hand, and on the other hand preventing generic competitors from undermining patented drug sales with impunity.

I. Introduction

Congress intended the Hatch-Waxman Act to promote two seemingly opposed policy goals: to incentivize and reward pharmaceutical companies for bringing new drugs to market; and to facilitate the availability of low-cost generic drugs. *See, e.g.*, *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1356 (Fed. Cir. 2003). The Hatch-Waxman Act added the ANDA process to the existing New Drug Application (''NDA''). NDA applicants must establish safety and efficacy before the FDA to gain approval to market and sell a drug to treat a human disease or condition. The ANDA process allows an applicant to rely on safety and efficacy data in a previously approved NDA instead of generating and submitting its own data. An ANDA applicant need only show bioequivalence to the so-called reference NDA. *Id.*

The Hatch-Waxman Act provides a detailed process by which a generic manufacturer can proceed to market before the expiration of any patents associated with an approved drug, for example by challenging their validity or showing non-infringement. NDA holders are required to list all patents that might reasonably be asserted against an infringer in the Orange Book, and ANDA applicants must certify some reason, such as invalidity or non-infringement, why the ANDA may proceed despite each listed patent. *See, e.g.*, Thomas, J. R., *Pharmaceutical Patent Law* (Arlington, Va.: Bloomberg BNA 3d ed. 2015) and 2016 Supp. (p. 537, Ch. 12); and 21 U.S.C. § 355(j)(1) and § 355(b)(2). Filing an ANDA application is defined as an ''act of infringement'' in 35 U.S.C. § 271(e)(2) that creates case or controversy jurisdiction in federal district court, even if, as is most often the case, the generic drug has not yet been manufactured or sold. See, *e.g.*, *Warner-Lambert*, 316 F.3d at 1363.

II. Using the Drug Label to Establish Induced Infringement Under the Hatch-Waxman Act

Infringement of method-of-treatment claims operates under a theory of induced infringement. Because generic manufacturers typically do not perform all the steps of a method-of-treatment claim, the branded pharmaceutical company typically sues the generic manufacturer under the theory that the ANDA will actively induce physicians and/or patients to infringe the claimed method. The proposed ANDA drug label is a critical piece of evidence in proving active inducement.

A. Specific Intent and the Drug Label

1. ''Skinny Labeling'' and Avoiding Infringement

Generally, the label for the generic version of an FDA-approved drug must be exactly the same as the FDA-approved drug label. 21 U.S.C. § 355(j)(2)(A)(v), (j)(4)(G); 21 C.F.R. § 314.94(a)(8)(iv). Skinny labeling is an exception to this rule by which a generic manufacturer makes a so-called ''section viii statement'' seeking FDA approval ***only*** for one or more uses not covered by a method patent (sometimes called a ''controlling use'' patent) listed in the Orange Book, along with a proposed label that ''carves out'' the patented method. 21 U.S.C. § 355(j)(2)(A)(viii). *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1046 (Fed. Cir. 2010); *Bayer Schering Pharma AG & Bayer HealthCare Pharms., Inc. v. Lupin, Ltd.*, 676 F.3d 1316 (Fed. Cir. 2012). The FDA will approve an ANDA with a section viii statement only if (1) there is no overlap between the proposed label submitted by the ANDA applicant and the use described in the Orange Book, and (2) removing the information pertaining to the patented method of use from the label does not render the drug less safe or effective. *See* 21 C.F.R. § 314.127(a)(7); *see also, Applications for FDA Approval to Market a New Drug*, 68 Fed. Reg. 36,676, 36,682 (June 18, 2003).

The ability of generic manufacturers to use skinny labeling to avoid infringement serves an important goal of the Hatch-Waxman Act, *i.e.* enabling the sale of affordable generic drugs for non-patented uses. *See Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S* 132 S. Ct. 1670, 1673 (''Congress understood [that] a single drug may have multiple methods of use, only one or some of which a patent covers'' and that the Hatch-Waxman Act ''contemplates that one patented use will not foreclose marketing a generic drug for other unpatented ones.''); *Warner-Lambert*, 316 F.3d at 1359 (the statute 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.'') Thus, to the extent **only off-label infringing uses** result from an ANDA, a patentee is generally out of luck under the Hatch-Waxman Act.

2. Requirement for Knowledge of the Patent and Specific Intent to Induce

The patentee can attempt to prove that the ANDA applicant is liable for inducing infringement despite the section viii statement. To establish liability, the patentee must prove that the defendants ''induced infringing acts and that [they] knew or should have known [their] ac-

tions would induce actual infringement.'' *Warner-Lambert*, 316 F.3d at 1363, citing *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990). More specifically, the patentee must prove by a preponderance of the evidence (1) knowledge of the asserted patent and (2) a specific intent to induce infringement. *Warner-Lambert*, 316 F.3d at 1363; *Global-Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060 (2011); *DSU Medical Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (*en banc* in relevant part). Constructive knowledge of the asserted patent is sufficient and can be proven by circumstantial evidence. *See, e.g., Bone Care Int'l, L.L.C. v. Roxane Labs., Inc.*, 2012 BL 143175 (D. Del. June 11, 2012). To establish the required specific intent, the drug label must do more than merely ''describ[e] the infringing mode'' and must ''teach an infringing use such that [the court is] willing to infer from those instructions an affirmative intent to infringe the patent.'' *Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp.,* 785 F.3d 625, 631 (Fed. Cir. 2015) (internal quotation marks omitted). This requires affirmative acts: ''[t]he label must **encourage, recommend, or promote infringement**.'' (emphasis added) *Id.* Evidence of the ''general prevalence'' of the infringing conduct is not required; in fact, if the instructions or warnings provide sufficiently clear promotion of infringing acts, ''it is irrelevant that some users may ignore the warnings in the proposed label.'' *AstraZeneca,* 633 F.3d at 1060. On the other hand, especially in cases where a product has ''substantial noninfringing uses,'' courts will not infer intent to induce infringement even when the defendant has actual knowledge that some users of its product may be infringing the patent. *Warner-Lambert,* 316 F.3d at 1365. In addition, ''vague'' instructions that require one to ''look outside the label to understand the alleged implicit encouragement,'' without more, do not induce infringement. *Takeda,* 785 F.3d at 632, 634.

B. Only FDA-Approved Uses Covered

As noted above, if the patented use is off-label, the patentee has no induced infringement cause of action under the Hatch-Waxman Act. Thus, one important route for a generic manufacturer to avoid liability is to show that the patented use is not the same ''use'' as that approved by the FDA.

In *Warner-Lambert*, the patent covering the FDA-approved use of gabapentin in treating partial seizures had expired, and Apotex sought an ANDA for such use. *Warner-Lambert,* 316 F.3d at 1352. Warner-Lambert asserted a patent claiming methods of treating neurodegenerative diseases. *Id.* The FDA had not approved gabapentin for neurodegenerative diseases, but Warner-Lambert alleged that the ANDA would induce infringement because three-quarters of prescriptions for gabapentin were for off-label uses, including treating neurodegenerative conditions. *Id.* at 1353. Furthermore, it argued that ''doctors, managed care organizations, and other institutions commonly and routinely substitute generic drugs for all indications for which the brand name drug is used,'' which would necessarily lead to infringing uses. *Id.* However, the district court granted Apotex's motion for summary judgment after discovery, and the Federal Circuit affirmed. *Id.* at 1353, 1366.

Construing for the first time the language of 35 U.S.C. § 271(e)(2)(A) that makes it an act of infringement to submit an ANDA, the Federal Circuit held that it is only an act of infringement to apply for an ANDA to make, use, or sell a drug if the drug or ***the use*** for which FDA approval is sought is claimed in a patent. *Id.* at 1354-55. Although it is now a matter of black-letter law that the patented ''use'' and FDA-approved ''use'' must be the same, claim language does not always exactly mirror the label language describing the approved use(s). Furthermore, the patent might claim the treatment of the FDA-approved use *in addition to* or *concurrently with* other uses, or even conditions *related to* the FDA-approved use. Thus, there is often a dispute as to whether the patent covers the same ''use.'' *See, e.g., Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S,* 132 S. Ct. 1670 (holding that generic manufacturers may counterclaim to have Orange Book ''use codes'' corrected if the patentee has attempted to define the patented ''use'' in an unjustifiably broad manner).

In *Bayer v. Lupin*, patent claims covering a method of treating three conditions *simultaneously*, only one of which was the approved use, were found not to support an induced infringement action, even though using the drug *necessarily* treated all three conditions simultaneously and the NDA label acknowledged that all three effects took place. *Bayer v. Lupin,* 676 F.3d 1316. Specifically, the asserted patent claims recited a ''method of simultaneously achieving, during premenopause or menopause a contraceptive [or gestagenic] effect, antiandrogenic effect, and an antialdosterone effect in a female patient'' by administering dihydrospirorenone (Yasmin®). *Id.* at 1320. The ANDA sought approval for use of the drug for contraception and not the other two claimed effects. *Id.* at 1319.

The court, citing its previous decisions in *Warner-Lambert* and *Allergan v. Alcon*, held that because the FDA had only approved Yasmin® for contraception, the asserted patent could not support the induced infringement claim for treating all three conditions simultaneously. *Id.* at 1326; *Allergan, Inc. v. Alcon Laboratories, Inc.,* 324 F.3d 1322, 1324 (Fed. Cir. 2003) (holding that a patent to methods of optic nerve protection and neural protection could not support an induced infringement claim where the only FDA-approved use was reducing intraocular pressure, even though administering the drug necessarily had all three effects in patients). The NDA label, taken as a whole, did not ''indicate to physicians that the specific use claimed'' of producing all three effects in women with a ''specific need of all three effects'' was safe and effective. *Id.*

C. Substantial Non-Infringing Uses Limit the Circumstances in Which Courts Will Infer Inducement

Even if the claimed method covers the uses for which an ANDA is sought, courts are less likely to infer intent to induce infringement if there are **substantial non-infringing** uses of the drug. Noninfringing uses are ''substantial'' if ''they are not unusual, far-fetched, impractical, occasional, aberrant, or experimental.'' *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009). In *Warner-Lambert*, the court refused to infer the required specific intent when merely 2.1percent of prescriptions for the ANDA drug would infringe. (The *Warner-Lambert* court held that the infringement suit could not proceed because the patent did not cover an FDA-approved ''use,'' but the court also considered

the inducement issue separately in case it arose later, for example if Apotex's ANDA were later approved by the FDA.) Warner-Lambert, 316 F.3d at 1363.*Warner-Lambert,* 316 F.3d at 1365; *see also*, *Acorda Therapeutics Inc. v. Apotex Inc.*, 2011 BL333949 (D.N.J. Sept. 6, 2011), *aff'd*, 476 F. App'x 746 (Fed. Cir. 2012) (finding that the defendant did not induce infringement because, *inter alia*, noninfringing uses were approximately 75 percent).

However, it is important to note that off-label uses, no matter how significant, do not constitute substantial non-infringing uses. Because a generic manufacturer may not market an ANDA product for off-label uses, it may not use evidence of off-label, non-infringing uses as ''substantial non-infringing uses'' to defeat a claim for induced infringement. *See, e.g., Depomed, Inc. v. Actavis Elizabeth LLC*, No. 12-1358 (JAP), at *44 (D.N.J. Aug. 18, 2014). This is entirely reasonable because if the patentee is limited to FDA-approved uses in showing inducement, it would be unfair for the generic manufacturer not to be limited in the same way for showing substantial non-infringing uses.

Notwithstanding the above, if the instructions to infringe are sufficiently clear, a defense of substantial non-infringing uses will not prevent the court from inferring intent to induce. For example, in *AstraZeneca v. Apotex*, discussed in further detail below, the court barely mentioned Apotex's defense of substantial non-infringing uses, focusing instead on the clear instructions to physicians to alter the drug dose over time in a manner that would lead inevitably to infringement. *AstraZeneca*, 633 F.3d at 1047. The ANDA sought approval for twice-daily dosing and the patent only covered once-daily or less frequent dosing; despite the substantial non-infringing uses (twice-daily dosing), the court found intent to induce infringement. *Id.* at 1059-60.

D. The Label Must Cross the Line From Providing Information or Warnings to Encouraging, Recommending, or Promoting Infringement

Drug labels must contain, *inter alia*, information on permitted uses, dosing, side effects, drug-drug interactions, and contraindications. Skinny labels must strike a balance between including enough information to satisfy the FDA while differentiating the skinny label from the NDA to avoid inducement. In general, courts are more willing to infer intent where the differentiation between the patented use and the ANDA use is unclear or small. In contrast, a skinny label is more likely to avoid infringement where it is possible to differentiate the information provided in the label from the patented use.

1. Merely Providing Warnings or Safety Information That May Allow for Infringing Uses Is Not Enough to Show Specific Intent

Courts have consistently required more than mere warning language or safety information in a label to find intent to induce infringement. *See, e.g., Takeda*, 785 F.3d 625, and *United Therapeutics Corp. v. Sandoz, Inc.*, 2014 U.S. Dist. 2014 BL 121573 (D.N.J. Aug. 29, 2014). For example, in *Takeda*, the skinny label successfully differentiated between use of the drug for **prophylactic treatment of gout** and **treatment of acute gout flares**.

Takeda asserted patents claiming a method of treating acute gout flares with two spaced, different doses of colchicine, a traditional medicine used for centuries. The proposed ANDA drug label carved out treatment of gout flares, seeking approval *only* for gout prophylaxis. *Takeda*, 785 F.3d at 628. Importantly, the label stated that the generic product was ''**indicated for prophylaxis**'' and that ''the safety and effectiveness of [it] **for acute treatment of gout flares during prophylaxis has not been studied.**'' (emphasis added) *Takeda*, 785 F.3d at 630. The label also instructed patients ''[i]f you have a gout flare while taking [Mitigare, the ANDA product], **tell your healthcare provider**.'' (emphasis added) *Id.* Takeda argued that the latter statement induced infringement because physicians would likely instruct patients to take the ANDA product for acute gout flares in a manner that would infringe the patented method of treatment. Remarkably, the FDA had even informed the defendant that ''it may be natural for the provider to use [Mitigare] for acute treatment.'' *Id.* at 632. Thus, as noted by the court, the defendant had actual knowledge that infringement was likely to result from its ANDA label. *Id.*

However, the court found that ''vague label language cannot be combined with speculation about how physicians may act to find inducement.'' *Id.* The court reasoned that such language did not amount to ''encouraging, recommending, or promoting'' infringement because it was neither an ''explicit or implicit instruction to take'' the ANDA product for the patented method. Furthermore, inferring infringement from such label language would too easily improperly transform mere knowledge of infringing uses into active inducement. *Id.* Although not explicitly addressed by the court, one might read the statement that the generic product was ''indicated for prophylaxis'' and treatment for acute treatment of gout flares ''has not been studied'' as clearly disclaiming the patented use (as opposed to simply omitting it) and might actually *discourage* physicians from practicing the patented method. It would discourage physicians from infringing the patent because stating treating of gout flares ''has not been studied'' implies that there would be some risk of unpredictable results if the medication were used in treating gout flares.

Furthermore, the court did not limit its inquiry to the four corners of the label. The court noted the ''host of alternatives'' for treating gout flares and that some of the alternatives such as corticosteroids and other anti-inflammatory agents were **preferred** over colchinine. *Id.* at 632-633. There was also insufficient record evidence that ''physicians would forego these alternatives and simply increase the dose of Mitigare when it failed to work as a prophylactic.'' *Id.* The court also considered Takeda's proffered declarations from physicians that it would be ''impractical'' for a physician not to suggest that a patient taking Mitigare for prophylaxis take an increased dose of Mitigare for a gout flare, but rejected them as insufficient to establish the inevitability of infringement. *Id.* at 633. The court concluded that ''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.'' *Id.* at 632. In looking outside the label and considering whether there were alternatives to the patented method, the court suggested that future cases might

turn on the existence of such alternatives. Where such alternatives are actually preferred to the patented method (like *Takeda*), it would be consistent with *Takeda* for courts to be less willing to infer active inducement.

In *United Therapeutics Corp. v. Sandoz*, warnings to the physician about the dangers of ***not*** diluting the drug product before injection were held not to induce infringement, even though the patent covered a method of treatment that recited diluting the drug with a particular diluent adapted for that drug. *United Therapeutics Corp. v. Sandoz, Inc.*, 2014 U.S. Dist. BL 121573. In *United*, the drug Remodulin® had been approved as an injectable for treatment of pulmonary arterial hypertension. However, injection of the undiluted drug solution caused intense pain at the injection site in a subset of patients. Eventually, United Therapeutics overcame this problem by developing a particular diluent solution, Flolan®, that also minimized the risk of bacterial blood infections in patients.

During the course of the litigation, Sandoz amended the ANDA to eliminate any mention of a diluent meeting the definition of Flolan® in the claim language above as an adjunct to therapy with Remodulin®. United nonetheless alleged that the warnings in the label were ''so unusual'' and ''so severe'' that they ''amount[ed] to an implicit instruction to physicians'' to dilute the ANDA product with the diluent recited in the claims. *Id.* at 36. The court took note of the fact that multiple sections of the label warned of the possibility of fatal blood infections and that the drug might have to be diluted. *Id.* at 43, 44. However, the label stated that ''[c]ontinuous subcutaneous infusion (undiluted) is the preferred mode. Use intravenous infusion (dilution required) if subcutaneous infusion is not tolerated.'' *Id.* However, the label specified that if dilution was required it ''must'' be performed with either sterile water or 0.9 percent sodium chloride injection diluent. *Id.* The court interpreted this label language as providing ''explicit, non-infringing instructions on how to reduce the risk of blood stream infections.'' *Id.* As for the warning language, the court found that it was not an implicit instruction to infringe the patent, reasoning that ''there is a rather significant difference between a warning and an instruction. A warning provides information regarding a potential risk. It does not prescribe a course of action. An instruction, on the other hand, is a statement directing one to take some action, such as how to avoid a potential adverse event.'' *Id.* at 49. Far from providing such instruction, the court found that physicians would have to engage in a ''a scholarly scavenger hunt'' to arrive at infringing acts based on the label. *Id.* at 50. Similarly, courts have held that labels that merely give ''permission'' for infringing uses do not provide sufficient instruction or direction to establish inducement. *See, e.g., Shire LLC v. Amneal Pharms., LLC,* No. 11-3781, 2014 U.S. Dist. BL 85369 (D.N.J. June 23, 2014) (noting the difference between ''permission'' and the ''encouragement'' required to show inducement, and granting summary judgment on the issue of inducement where the accused product package insert could, at most, ''be understood to permit an infringing use''); *Aventis Pharma Deutschland GmbH v. Cobalt Pharms., Inc.*, 355 F. Supp. 2d 586, 598-99 (D. Mass. 2005). *United* and similar cases thus show that drafting potentially problematic label language as warnings or safety information instead of instructions for use can help persuade a court not to infer intent to induce infringement.

Subsequent cases have reinforced the distinction between mere warnings and information, which are usually insufficient to establish inducement, versus instructions to perform infringing acts. In *Otsuka v. Torrent Pharmaceuticals*, a consolidated action stemming from the flurry of ANDA applications filed around the expiration in April of 2015 of the initial patents covering the blockbuster drug aripiprazole (Abilify®; U.S. sales of $6.4 billion in 2013), the district court denied Otsuka's motion for a temporary restraining order and preliminary injunction because Otsuka was unlikely to succeed on its induced infringement claims. *Otsuka Pharm. Co., LTD. v. Torrent Pharms. Ltd., Inc.*, 99 F. Supp. 3d 461 (D.N.J. 2015). At the time of the dispute, Otsuka had only follow-on patents relating to aripiprazole, and so its ability to preclude generic competition hinged on showing induced infringement of its remaining patents. *Otsuka Pharm. Co.* 99 F. Supp. 3d. 461, 468. Otsuka asserted a patent covering a composition comprising a *combination* of aripiprazole and escitalopram or citalopram, alleging that the ANDAs would induce infringement. *Id.*

Each ANDA applicant sought approval for a generic product containing ***only*** aripiprazole as active ingredient. *Id.* at 469. However, Otsuka argued that the warning and safety information in the ANDA labels concerning the co-administration of aripiprazole with antidepressants, particularly in the defendants' ''black box'' warnings, ''implicitly'' taught and encouraged the beneficial results of co-administering aripiprazole in the manner claimed in the patent, *i.e.* with serotonin reuptake inhibitors such as escitalopram and/or citalopram. *Id.* at 476. The court nonetheless denied Otsuka's motion for a temporary restraining order because Otsuka had failed to establish a likelihood of prevailing on its induced infringement claim because the defendants had carved out any mention in their labels of adjunctive therapy, effectively disclaiming the patented use. *Id.* at 485. Furthermore, by relying on the warnings and safety information in the labels for its inducement claims, Otsuka was ''rel[ying] upon contraindications and language tending to warn about aripiprazole's potential effects and/or adverse reactions/interactions. **But, a warning is just that—a warning. It is not an instruction to coadminister aripiprazole with any particular drug, much less escitalopram or citalopram, the only antidepressants covered by Claim 1.**'' (emphasis added) *Id.* at 490.

Notably, the court also considered exactly where in the label the supposedly inducing language appeared, noting that ''the weight of authority has deemed warning and safety information insufficient to constitute inducement, requiring instead that the information be set forth in the ''Uses and Indication'' or ''Dosing and Administration'' sections of the allegedly offending labels.'' (citations omitted) *Id.* at 492.

2. Warnings and Safety Information That Lead Inevitably to Infringement May Still Induce Infringement

However, even language characterized by courts as a ''warning'' can induce infringement if the language, in reality, provides **directions or instructions** that ***inevitably*** lead to infringement. For example, in *AstraZeneca v. Apotex*, the asserted claims were directed to a

method of treating respiratory diseases that involved administering a budesonide composition **not more than once daily**. *AstraZeneca*, 633 F.3d at 1046-1047. Apotex submitted an ANDA for a generic version of budesonide for **twice-daily** use that included a section viii statement that they were carving out once-daily use. *Id.* at 1047. The FDA stated in a letter to Apotex that the proposed label ''did not teach'' the infringing use. *Id.* at 1057. Furthermore, the FDA stated that the ''weight of the evidence is stronger in support of efficacy for twice[-]daily dosing as opposed to once[-]daily dosing...omission of once-daily dosing in the generic BIS labeling would not render the generic drug less safe or effective. . . .'' *Id.* Based on these facts, Apotex argued that there were substantial non-infringing uses for the drug (*e.g.*, twice-daily administration for asthma). *Id.* at 1047. However, Apotex's ANDA label, just like the NDA drug label, included a mandatory warning to ''titrate down'' to the lowest effective dose to avoid the adverse effects from excessive use of the drug. *Id.* The warning appeared repeatedly throughout the label, including in the ''Dosage and Administration'' and ''Precautions'' sections. *Id.* The court noted that Pulmicort Respules®, the approved budenoside drug, was sold in single-dose vials that had to be used as soon as they were opened, and the ANDA label sought approval for strengths of 0.25 or 0.5 mg per 2 mL vial, **the same strengths as the NDA**. *Id.* at 1057. The district court considered that, given the downward dose titration warning, the first logical step downward from 0.5 mg twice a day would be to use 0.25 mg once a day. *Id.* There was no approved 0.125 mg dose vial—nor did the ANDA seek such approval—so there would have been no way, for example, to take 0.125 mg twice a day to arrive at a 0.25 mg/day total dose. *Id.*

The Federal Circuit affirmed the district court's grant of a preliminary injunction, emphasizing that for induced infringement the ''pertinent question is whether the proposed label **instructs** users to perform the patented method.'' (emphasis added) *Id.* at 1059. The court rejected Apotex's arguments because, even if some physicians or users would be expected to ignore the warning, the label language was still an instruction that would ***necessarily*** lead to infringement. *Id.* Importantly, the court reached its holding despite the fact that there were substantial non-infringing uses for the product. *Id.* Instead, the court took Apotex to task for failing to attempt to craft a non-infringing label because, for example, faced with the knowledge that downward titration from 0.5 mg twice daily would lead to infringement, Apotex could have sought approval for a 0.125 mg vial for twice-daily administration. *Id.*

At first glance, *AstraZeneca* appears somewhat at odds with the *United*, *Otsuka*, and *Takeda* line of cases. After all, the ANDA sought approval only for non-infringing conduct (twice a day dosing) and the label did no more than warn that downward dose titration was required to avoid adverse effects. Similarly, in *United*, the label simply warned of the possibility of blood infections and that dilution was sometimes necessary. The ANDA label in *Otsuka* included warnings about aripiprazole's interactions with other drugs. However, *AstraZeneca* may be distinguished from *United* and *Otsuka* because downward dose titration led ***inevitably*** from twice a day to once a day to result in infringing conduct. There was no such inevitability in *United* and *Otsuka* because it was straightforward to comply with the warnings and use alternatives to the infringing conduct. It appears, then, that courts are only willing to infer the specific intent to induce infringement when there is an element of inevitability—not merely the possibility—associated with the infringing action. Such inevitability may result from clear instructions to infringe in the label and/or where there are a lack of alternatives to the infringing conduct. In such cases, even a ''warning'' is read as providing a clear instruction to infringe. Indeed, mere ''information'' can be sufficient to support an inference of intent to induce infringement. *See Sanofi v. Watson Laboratories Inc.*, 875 F.3d 636, 645 (Fed. Cir. 2017) (''[Where a label] directs medical providers to information identifying the desired benefit for only patients with the patent-claimed risk factors'' and ''[a]pproximately 77% of Multaq® prescriptions have actually been written for patients with the claimed risk factors,'' the district court did not err in drawing the required inducement inferences. It is important to note that the alternatives are evaluated in the context of the claim language. Where the claim language recites a dosing regimen or specialized dilution solution, for example, courts have looked carefully for the existence of alternative dosing regimens or dilution solutions.

As a hypothetical, consider the result if the ANDA label in *AstraZeneca* had sought approval only for dosing twice-daily, included the same mandatory downward titration language, and sought approval for an additional dosage strength option such as 0.125 mg per 2 mL vial. In this case, physicians would have been able to decrease the daily dose from 0.5 mg without having to go to a once-daily dose. Based on the court's reasoning above and the related case law, the *AstraZeneca* court would likely have held that the label did not induce infringement.

3. Even When the Patient Performs Some of the Steps of the Patented Method, Physician Control of the Patient May Lead to Inducement Under Principles of Agency and Control

In the recent decision in *Eli Lilly v. Teva*, the Federal Circuit found that warning language directing the physician to withhold treatment with pemetrexed unless the patient took two common vitamins before taking the anticancer agent pemetrexed induced physicians to infringe the patent. *Eli Lilly & Co. v. Teva Parental Meds., Inc.*, 845 F.3d 1357, 1361 (Fed. Cir. 2017). Eli Lilly discovered that pretreatment with folic acid and a methylmalonic acid lowering agent (*i.e.*, vitamin B12) reduced the toxicity of pemetrexed in patients. The patent in suit claimed a ''method of administering pemetrexed disodium to a patient in need thereof comprising administering **an effective amount of folic acid and an effective amount of a methylmalonic acid lowering agent *followed by administering*** an effective amount of pemetrexed disodium. . .'' (emphasis added) *Id.* at 1362. The FDA required the ANDA label to copy repeated warnings and instructions regarding the importance of and reasons for the pretreatment. *Id.* at 1366. In fact, the label directed physicians to withhold pemetrexed unless patients completed the pretreatment, and there was abundant evidence showing that physicians in actual practice made completion of the pretreatment an absolute condition of pemetrexed therapy. *Id.*

Given this situation, the court held that physicians exercised ''direction or control'' over patients such that

their actions were attributable to physicians, thus avoiding what would otherwise be divided infringement. *Id.* at 1367-68; *see Akamai Technologies, Inc. v. Limelight Networks, Inc. (Akamai V)*, 797 F.3d 1020, 1022 (Fed. Cir. 2015) (*en banc*) (*per curiam*), cert. denied, 136 S. Ct. 1661, 194 L. Ed. 2d 767 (2016) (directing or controlling others' performance includes circumstances in which an actor: (1) ''conditions participation in an activity or receipt of a benefit'' upon others' performance of one or more steps of a patented method, and (2) ''establishes the manner or timing of that performance.'')

Eli Lilly is a landmark decision for extending the situations in which intent to induce may still be inferred despite some steps of a method claim being performed by a physician and others by a patient. The decision directs courts to look past the technicalities of the physician performing some method steps and the patient other steps to the substance of the doctor-patient relationship, in which direction or control is necessary in many medical treatments.

As a matter of public policy, *Eli Lilly* prevents generic manufacturers from unfairly avoiding liability merely because more than one party carries out their instructions to infringe a method-of-treatment patent. It would be unfair to patentees to refuse to infer intent to induce in situations like *Eli Lilly*, when the nature of the claimed method of treatment required administration of several drugs. Indeed, it would be difficult to imagine a scenario in which all such method steps would be performed by a single party.

III. Conclusion

The legal framework around induced infringement analyses in the ANDA context has evolved into a flexible means for courts to balance competing public policy concerns. The outcomes of these cases are fact-specific due to the dependence of drawing the required inference (or not) based on the actual uses and effects of the drug in question, the FDA's findings on safety and efficacy, and above all the exact language of the drug label. Nonetheless, both branded and generic pharmaceutical companies may draw guidance from this legal framework to inform their patent and business strategies. Courts parse proposed ANDA drug labels to look for something more than warnings or information, such as active instructions or encouragement to perform the infringing acts. Courts appear to find inducement most often where there is an element of inevitability of resulting infringement. Accordingly, generic manufacturers are well-advised to leave non-infringing options to physicians and tread carefully where the FDA requires dose titration or other mandatory warnings that lead directly to any patented dosage or treatment regimens. Leaving non-infringing options might mean seeking approval of other dose strengths or diluent solutions or administration methods, as in *AstraZeneca* and *United*, above. Branded pharmaceutical companies should seek to embody as closely as possible the approved label language in their patent claims to force generic competitors to adopt label language that instructs physicians to infringe despite the attempt at skinny labeling.