Labeling and Induced Infringement in Pharma Patent Litigation and Protecting IP Rights

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35 U.S.C. § 271

a) Except as otherwise provided in this title, whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States, or imports into the United States any patented invention during the term of the patent therefor, infringes the patent.

b) Whoever actively induces infringement of a patent shall be liable as an infringer.
General Principles: Inducement Involves a Two-Prong Analysis

1. Direct infringement by an actor; and

2. Specific intent to induce infringement by another.
General Principles: Divided Infringement

Akamai Techs., Inc. v. Limelight Networks, Inc., 797 F.3d 1020 (Fed. Cir. 2015)

In cases of divided infringement, one entity could be liable for direct infringement under two circumstances:

- Entity directs or controls another entity’s performance.
  - Acts through agency or contractual relationship;
  - Conditions participation in an activity or receipt of a benefit upon performance of a step or steps of a patented method and establishes the manner or timing of that performance.

- Entities form a joint enterprise.
General Principles: The Role of A Reasonable Belief As A Defense


• A reasonable belief of non-infringement is a defense to claims of inducement, but a good faith belief that a patent is invalid is not a defense to a charge of induced or contributory infringement.
Proving induced infringement:

- “Accordingly, we now hold that induced infringement under §271(b) requires knowledge that the induced acts constitute patent infringement.” Global-Tech Appl., Inc. v. SEB S.A., No. 10-6 (May 31, 2011).

  - Patentee must show accused infringer knew of the patent.

  - Patentee must show accused infringer intended its actions to cause direct infringement.
General Principles: Willful Blindness


• Willful blindness can substitute for actual knowledge.
  — “Given the long history of willful blindness and its wide acceptance in the Federal Judiciary, we can see no reason why the doctrine should not apply in civil lawsuits for induced patent infringement....”

• Two basic requirements: (1) the defendant must subjectively believe that there is a high probability that a fact exists and (2) the defendant must take deliberate actions to avoid learning of that fact.
General Principles:
Intent in Hatch-Waxman Act Cases

• Knowledge of the patent.
  • Easily shown by the patents listed in the Orange Book and the generic manufacturer’s paragraph IV certification.

• Knowledge that accused infringer intended its actions to cause direct infringement.
  • May be established by the instructions and information in a drug label.
General Principles: Carve-outs in Hatch-Waxman Act Cases

The “Skinny viii” Option

- An ANDA filer can omit, or “carve out,” a patented indication from its labeling to avoid having to file a paragraph IV certification on the patent(s) that cover that indication.
  - 21 U.S.C. § 355(j)(2)(A)(viii) allows ANDA applicant to submit, in lieu of a paragraph IV certification, a certification that an Orange Book listed patent does not claim an indication for which the ANDA applicant seeks FDA approval.

- Does the labeling still encourage, recommend, or promote the allegedly carved-out use?
Matching Label to Claim

- **Eli Lilly & Co. v. Teva Parenteral Medicines, Inc., 845 F.3d 1357 (Fed. Cir. 2017)**

- Claim 1. 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 [vitamin B12]
  - followed by administering an effective amount of pemetrexed disodium....

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**DOSAGE AND ADMINISTRATION**

- The recommended dose of ALIMTA, administered as a single agent or with cisplatin, in patients with creatinine clearance of 45 mL/minute or greater is 500 mg/m² as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. (2.1, 2.2, 2.3)
- Initiate folic acid 400 mcg to 1000 mcg orally, once daily, beginning 7 days prior to the first dose of ALIMTA and continue until 21 days after the last dose of ALIMTA. (2.4)
- Administer vitamin B₁₂, 1 mg intramuscularly, 1 week prior to the first dose of ALIMTA and every 3 cycles. (2.4)
- Administer dexamethasone 4 mg orally, twice daily the day before, the day of, and the day after ALIMTA administration. (2.4)
**Steps**

- **Teva**
  - Supplies the pemetrexed

- **Patient**
  - Self-administers folic acid

- **Physician**
  - Administers B12 & pemetrexed
**Label: Indications and Usage**

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**INDICATIONS AND USAGE**

ALIMTA® is a folate analog metabolic inhibitor indicated for the:

- initial treatment of patients with locally advanced or metastatic non-squamous, non-small cell lung cancer (NSCLC) in combination with cisplatin. (1.1)
- maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy, as a single agent. (1.1)
- treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy, as a single agent. (1.1)

Limitations of Use:
ALIMTA is not indicated for the treatment of patients with squamous cell NSCLC. (1.1)

- initial treatment, in combination with cisplatin, of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery. (1.2)
Label: Patient Information

PATIENT INFORMATION
ALIMTA® (uh-LIM-tuh)
(pemetrexed for injection)

How is ALIMTA given?

- It is very important to take folic acid and vitamin B₁₂ during your treatment with ALIMTA to lower your risk of harmful side effects.
  - Take folic acid exactly as prescribed by your healthcare provider 1 time a day, beginning 7 days (1 week) before your first dose of ALIMTA and continue taking folic acid until 21 days (3 weeks) after your last dose of ALIMTA.
  - Your healthcare provider will give you vitamin B₁₂ injections during treatment with ALIMTA. You will get your first vitamin B₁₂ injection 7 days (1 week) before your first dose of ALIMTA, and then every 3 cycles.
- Your healthcare provider will prescribe a medicine called corticosteroid for you to take 2 times a day for 3 days, beginning the day before each treatment with ALIMTA.
- ALIMTA is given to you by intravenous (IV) infusion into your vein. The infusion is given over 10 minutes.
- ALIMTA is usually given 1 time every 21 days (3 weeks).
**Direct Infringement Required**

**District Court:** Claims valid and infringed.
- No single actor performs all steps of the asserted claims -- actions of both physicians and patients are required.
- But all steps of the asserted claims are attributable to physicians, so court found direct infringement attributable to physicians.

**Federal Circuit:** Affirmed.
- “Where, as here, no single actor performs all steps of a method claim, direct infringement only occurs if ‘the acts of one are attributable to the other such that a single entity is responsible for the infringement.’” Akamai V, 797 F.3d at 1022. The performance of method steps is attributable to a single entity in two types of circumstances: when that entity ‘directs or controls’ others’ performance, or when the actors ‘form a joint enterprise.’”
**Must Also Show Specific Intent for Induced Infringement**

- **District Court: Induced infringement.**
  - “Defendants induce physicians’ infringement because physicians act “in accordance with Defendants’ proposed labeling.”

- **FC: Affirmed.**
  - “[T]he intent for inducement must be with respect to the actions of the underlying direct infringer, here physicians.”

  - “When the alleged inducement relies on a drug label’s instructions, ‘[t]he question is not just whether [those] instructions describ[e] the infringing mode, ... but whether the instructions teach an infringing use such that we are willing to infer from those instructions an affirmative intent to infringe the patent.’ ... ‘The label must encourage, recommend, or promote infringement.’”

  - In this case, “[t]he instructions are unambiguous on their face and encourage or recommend infringement.”
Lessons Learned from Eli Lilly

• Inducement and divided infringement can live together happily ever after.

• Accused infringer can instruct direct infringer to infringe, who in turn directs another actor to carry out some of the infringing steps.

  • Accused infringer intends to cause direct infringer to perform acts that are known to infringe.

  • Attribution of all method steps to the direct infringer.
Lessons Learned from Eli Lilly

• In Hatch-Waxman Act cases relying on the ANDA filer’s proposed labeling to show inducement, the issue of specific intent often turns on whether the proposed labeling instructs users to perform the patented method.

• The labeling must encourage, recommend, or promote infringement.

• Even where the labeling does not explicitly recite the claim limitations, instructions that inevitably lead some users to practice the claimed method is sufficient evidence of specific intent.
Instructions to Establish Intent

AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042 (Fed. Cir. 2010)

- AstraZeneca’s Pulmicort Respules (budesonide inhalation suspension) approved in 2000.

- Indicated for maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age.

- Each respule is a plastic vial containing a single dose of budesonide suspended in sterile liquid.

- Drug is administered by squeezing the entire contents of a vial into a jet nebulizer and inhaling the resulting mist through a mask attached to the nebulizer.
Instructions to Establish Intent

AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042 (Fed. Cir. 2010)

• Dosing recommendations:
  
  • Bronchodilators alone: 0.5 mg once daily or 0.25 mg twice daily
  • Inhaled corticosteroids: 0.5 mg once daily or 0.25 mg twice daily up to 0.5 mg twice daily
  • Oral corticosteroids: 0.5 mg twice daily or 1 mg once daily

In symptomatic children not responding to non-steroidal therapy, a starting dose of 0.25 mg once daily may be considered. If once-daily treatment does not provide adequate control, the total daily dose should be increased and/or administered as a divided dose. In all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved.
Instructions to Establish Intent

AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042 (Fed. Cir. 2010)

• Orange Book

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• ’603 patent method claims 1-28
  — Once-daily administration
  — 1. A method of treating a patient from a respiratory disease, the method comprising administering to the patient a nebulized dose of a budesonide composition in a continuing regimen at a frequency of **not more than once per day**.
Instructions to Establish Intent

_AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042 (Fed. Cir. 2010)_

- AstraZeneca filed a citizen petition with the FDA in 2008 concerning an ANDA submitted by IVAX Pharmaceuticals, Inc.

- In response, FDA issued a letter explaining that the labeling for a generic budesonide inhalation suspension could omit references to once-daily dosing and that the downward-titration language would be appropriate because the language did not “teach” once-daily dosing.

- FDA letter noted that “[t]itration to the lowest effective dose may involve, for example, a twice-daily regimen, once-daily dosing, or even alternate day dosing.”
Instructions to Establish Intent

AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042 (Fed. Cir. 2010)

• Apotex submitted ANDA seeking approval to market a generic budesonide drug for **twice-daily** use.

• Proposed label nearly identical to Pulmicort Respules label and IVAX’s label.
  - Retained the FDA-mandated downward-titration language.
  - FDA rejected attempt to insert “by administration twice-daily” in the label.

• Section viii statement that not seeking approval for once-daily method.

• Approved on March 30, 2009.
  - FDA rejected proposal after approval to add “twice daily” to the downward-titration language, add language that the drug was not approved for less than twice-daily use, and remove the downward-titration language.
Instructions to Establish Intent

*AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042 (Fed. Cir. 2010)

- AstraZeneca brought declaratory judgment action against Apotex in the District of New Jersey.

- Moved for a preliminary injunction barring Apotex from distributing its generic budesonide drug.
  - Argued that Apotex would induce infringement of method claims 1-3, 6-8, 11-18, and 21-28.
  - Downward-titration statements in proposed label effectively instructed consumers to use the drug once daily.

- After 5-day hearing, district court granted motion.
  - Determined that the proposed label would cause some users to infringe.
  - Found that Apotex was aware of the potential infringement problem and had other options that it decided not to pursue.
Instructions to Establish Intent

AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042 (Fed. Cir. 2010)

• On appeal, Apotex argued that its distribution failed to show that it possessed specific intent to infringe.

  — Argued that warnings on drug labels do not influence how a drug is used.

  — Argued that the proposed label was not enough to show specific intent because the FDA required it to include the downward-titration language in the label.

  — Argued that it never believed that the downward-titration language taught the claimed once-daily administration.
Instructions to Establish Intent

AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042 (Fed. Cir. 2010)

• Federal Circuit affirmed grant of preliminary injunction.
  – “[L]iability for active inducement may be found where evidence goes beyond a product’s characteristics or the knowledge that it may be put to infringing uses, and shows statements or actions directed to promoting infringement.”
  – “[E]vidence of active steps...taken to encourage direct infringement, such as advertising an infringing use or instructing how to engage in an infringing use, show an affirmative intent that the product be used to infringe.”
  – “The district court correctly concluded that such evidence exists here.”
  – “In the context of specific intent, it is irrelevant that some users may ignore the warnings on the proposed label. The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of Apotex’s affirmative intent to induce infringement.”
  – “The district court’s specific intent finding was not based solely on the proposed label, but also on Apotex’s decision to proceed with its plan to distribute the drug despite being aware that the label presented infringement problems.”
Instructions to Establish Intent

*AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042 (Fed. Cir. 2010)

  - Consolidated with related actions against other defendants.
  - Judgment in favor of defendants.
    - Dismissed claims 6, 11, 18, and 21-23 with prejudice because dropped at trial.
    - Found that defendants would induce infringement of claims 1-3, 7, 8, 12-17, and 24-28.
    - But determined that these asserted claims were invalid as obvious and anticipated.
  - 542 Fed. App’x 971 (Fed. Cir. 2013)
    - Affirmed obviousness determination.
Instructions to Establish Intent

*Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316 (Fed. Cir. 2012)

- Bayer’s Yasmin (drospirenone/ethinyl estradiol) tablets approved in 2001.

- Indicated for use by women to prevent pregnancy.

- Clinical Pharmacology
  
  **12.2 Pharmacodynamics**
  
  Drospirenone is a spironolactone analogue with *anti-mineralocorticoid activity*. The estrogen in Yasmin is ethinyl estradiol (EE).
  
  — Previously also stated that “[p]reclinical studies in animals have also shown that drospirenone has *anti-androgenic activity*”
Instructions to Establish Intent

*Bayer Schering Pharma AG v. Lupin, Ltd., 676 F.3d 1316 (Fed. Cir. 2012)*

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- U.S. Patent No. 5,569,652
  - Method claims for achieving three effects simultaneously
  - 11. A method of simultaneously achieving, during premenopause or menopause, a contraceptive effect, an anti-androgenic effect, and an antialdosterone effect in a female patient in need thereof....
Instructions to Establish Intent

*Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316 (Fed. Cir. 2012)

- Watson, Sandoz, and Lupin submitted ANDAs seeking approval to market generic drospirenone/ethinyl estradiol drugs for oral contraception.

- Filed paragraph IV certifications as to ’652 patent.

- Bayer sued in the Southern District of New York.

- District court granted motion by Watson and Sandoz for judgment of noninfringement on the pleadings under Federal Rule of Civil Procedure 12(c).

- Based on that ruling, Bayer and Lupin stipulated to final judgment against Bayer.
Instructions to Establish Intent

*Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316 (Fed. Cir. 2012)

- On appeal, Federal Circuit noted undisputed issues:
  - Bayer does not have patent protection for the use of the drug for contraception alone.
  - The claims are for simultaneously achieving three effects.
  - The only indication proposed in the NDA and set forth in the indications section of Yasmin’s label was oral contraception.
  - The proposed labels for the generic drugs used the same indications language and did not refer to the other two effects.
  - The patent can be infringed only if seeking approval to market the generic drug for the three simultaneous effects.

- Bayer argued that the FDA approved the use of Yasmin for all three effects and that the defendants were seeking approval for all three effects
  - Argued that the label instructs the use of the drug to obtain the three effects.
Instructions to Establish Intent

Bayer Schering Pharma AG v. Lupin, Ltd., 676 F.3d 1316 (Fed. Cir. 2012)

• Bayer relied on four pieces of evidence:
  – FDA regulation addressing the listing of patents in the Orange Book.
    – Argued that it requires submission of patents claiming indications and patents claiming other indications of use.
  – A declaration by a physician who prescribes Yasmin.
    – Stated that prescribing Yasmin as an oral contraceptive with the intent to produce the other two effects “is clearly stated and on-label.”
  – A declaration by a former FDA official who oversaw the approval of the Yasmin NDA.
    – Stated that the Yasmin label indicates that the FDA approved Yasmin for the other two effects.
    – Stated that listing the other two effects in the Clinical Pharmacology section indicated they were “pertinent” to human use.
  – Marketing materials for Yasmin that were approved by the FDA.
    – Highlighted the other two effects.
Instructions to Establish Intent

*Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316 (Fed. Cir. 2012)

- Federal Circuit affirmed dismissals:
  - “[W]hile the label mentions potential anti-mineralocorticoid and anti-androgenic activity, it does not do so in any way that recommends or suggests to physicians that the drug is safe and effective for administration to patients for the purposes of inducing these effects.”
  - “[T]he point is not simply that the method of use was not described in the Indications and Usage section...; 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.”
  - “[The] evidence...demonstrates only that the FDA was aware that Yasmin could cause the effects discussed in the ’652 patent....Absent [a] finding of safety and efficacy, and the recognition of such safety and efficacy on the Yasmin label, the Yasmin label cannot instruct (and the ANDA proposed label cannot induce infringement of) the method of use claimed in the ’652 patent.”
Instructions to Establish Intent

*Bayer Schering Pharma AG v. Lupin, Ltd., 676 F.3d 1316 (Fed. Cir. 2012)*

- Judge Newman dissented

  - “My colleagues err in endorsing this dismissal, which is contrary not only to the Federal Rules and judicial precedent, but also to the premises of FDA generic drug practices and to the purposes of the Hatch-Waxman Act.”

  - “The panel majority is incorrect in its statement that the safety and efficacy of the anti-androgenic and anti-mineralocorticoid effects were never reviewed by the FDA. The Clinical Pharmacology section of the Yasmin label discusses these effects of the active ingredient drospirenone....”

  - “The evidence before the district court...supported the statement in Bayer's complaint that a ‘significant proportion of drospirenone and ethinylestradiol prescriptions are written with the intent of producing three pharmacological effects—gestagenic, anti-aldosterone, and anti-androgenic.’ Even were these threshold facts disputed—and they were not—it is improper for a court to make contrary findings under Rule 12(c).”
Instructions to Establish Intent


- Takeda’s Colcrys (colchicine) tablets approved in 2009 for the prophylaxis and treatment of gout flares in adults.
**Instructions to Establish Intent**

*Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp., 785 F.3d 625 (Fed. Cir. 2015)*

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- Acute gout patents (’649 and ’938) for methods of treating acute gout flares.

Instructions to Establish Intent


- Hikma submitted 505(b)(2) application seeking approval to market a colchicine drug (Mitigare) for prophylaxis of gout flares.

- Did not include a paragraph IV certification.
  - Instead, relied on prior FDA findings of safety and efficacy concerning colchicine and did not seek approval for a use covered by Takeda’s patents.

- Approved in 2014.
  - Hikma launched Mitigare on October 3, 2014.
  - Planned to launch approved generic of Mitigare on October 10, 2014.
Instructions to Establish Intent


• Takeda sued Hikma in the District of Delaware.

• District court granted Takeda’s request for a temporary restraining order restraining Hikma from selling Mitigare and from launching a generic colchicine product.
  — Also restrained Takeda from launching an authorized generic version of Colcrys and required that Takeda provide 10-days notice to Hikma before the launch of any authorized generic of Colcrys.

• District court denied Takeda’s motion for preliminary injection.
  — Takeda did not show a likelihood of success on the merits for its induced infringement claims or irreparable injury.
Instructions to Establish Intent


- On appeal, Takeda argued that the Mitigare label induced infringement of the acute gout patents.
  - “If you have a gout flare while taking [Mitigare], tell your healthcare provider.”
  - Argued that a physician would likely tell a patient taking Mitigare for prophylaxis to use it to treat the acute flare.
Instructions to Establish Intent


- Federal Circuit affirmed denial of preliminary injunction

  - “The question is not just whether the instructions ‘describ[e] the infringing mode,’ 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.’**

  - “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.”

  - “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.”
**Instructions to Establish Intent**


- Federal Circuit affirmed denial of preliminary injunction
  
  - “[V]ague 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’—mere knowledge of infringing uses—into induced infringement.”

  - “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.”
Instructions to Establish Intent


• On appeal, Takeda also argued that the Mitigare label induced infringement of the DDI patents.
  — Label suggests that if coadministration “is necessary, the dose of Mitigare should be reduced and the patient should be monitored carefully for colchicine toxicity.”
  — Argued that a healthcare provider would have to determine whether coadministration was necessary and then follow the patented methods.
  — Physician declarations that he would “typically” follow Takeda’s patented methods if it was necessary to co-administer colchicine and medications “such as” those in the claims.

• Federal Circuit did not reach question of induced infringement because “there was insufficient proof of direct infringement.”
Label Does Not Have to Recite All Claim Limitations


- Actavis filed an ANDA for generic Contrave®
- ‘195 Patent Claim 11. A method of treating overweight or obesity having reduced adverse effects comprising orally administering daily about 32 mg of naltrexone and about 360 mg of bupropion ... to a person in need thereof, ... wherein the naltrexone ... is administered as a sustained-release formulation, and wherein said sustained-release formulation of naltrexone has an in vitro naltrexone dissolution profile ... of:
  a) between 39% and 70% of naltrexone released in one hour;
  b) between 62% and 90% of naltrexone released in two hours; and
  c) at least 99% in 8 hours ....
**Label Does Not Have to Recite All Claim Limitations**

**Orexigen v. Actavis**

- District Court: Induced infringement of claim 11.

  - Patient performs the single step of the claim, “administering” naltrexone and bupropion.

  - Defendant argued, *inter alia*, that Plaintiff cannot prove infringement because its proposed labeling does not mention the dissolution profile of its product.
Label Does Not Have to Recite All Claim Limitations

Orexigen v. Actavis

• District Court: Induced infringement of claim 11.

• District court: It is not necessary for the label to recite the claimed dissolution profile.

• “Defendant’s product meets all limitations in the claim and the label instructs on administering the product in the amount and with the frequency recited in the claim. Whether the patient who performs the method by administering the tablets knows that the tablets meet the dissolution profile is irrelevant for the purposes of infringement. Defendant knows that the tablets meet all of the claim limitations and, through its proposed label, encourages patients to administer the tablets in a manner that infringes the claimed method.”
Label “Actively Encouraged” Performance of the Sole Method Step

Orexigen v. Actavis

• ‘626 Patent Claim 25. A method of treating overweight or obesity, comprising administering a weight loss effective amount of a first and second compound to an individual who has been diagnosed as suffering from overweight or obesity in order to treat said overweight or obesity, wherein said first compound is bupropion, ..., and said second compound is naltrexone, ...

• Claim 26: naltrexone and bupropion “are administered together;” Claim 31: naltrexone and bupropion “are administered in a single oral dosage form.”
Label “Actively Encouraged” Performance of the Sole Method Step

Orexigen v. Actavis

- District court: No divided infringement.
  
  - The only step is “administering;” there is no separate “diagnosing” step.
    
    - Diagnosis is required, but it is not a separate step in the claimed method.
    
    - The individual will already be diagnosed prior to the method being performed.
Label “Actively Encouraged” Performance of the Sole Method Step

Orexigen v. Actavis

- District court: Induced infringement of claims 26 and 31.

  - “Actavis’s ANDA instructs physicians (or other healthcare provider) to diagnose an individual as suffering from overweight or obesity by determining that the individual has a body mass index (‘BMI’) of at least 27 kg/m².”

  - “Through its label, Defendant actively encourages patients to practice each element of the claimed method of [claims 26 and 31] by administering Defendant’s ANDA Product to themselves in accordance with the limitations of [claims 26 and 31].”
The Importance of Claim Construction


- Defendants filed ANDAs on generic versions of Novartis’s Zortress®

- Claim at issue:
  - Methods for treating or preventing transplant rejection comprising co-administering synergistically effective amounts of cyclosporin A (or tacrolimus) and everolimus in the weight ratio 2:1 to 180:1.

- Defendants conceded that their proposed labels teach all claim limitations except the synergistic effectiveness element.
  - Argued that coadministration of everolimus and cyclosporin A/tacrolimus as instructed by the label would not be synergistically effective.
  - Argued that synergy must be assessed using the Berenbaum-Chou equation.
The Importance of Claim Construction

Novartis v. Breckenridge

• District Court: Induced infringement.
  • Defendants never argued that “synergistically effective” requires reliance on the Berenbaum-Chou equation.

• District Court construed term to mean “amounts which are individually equal to or below their respective effective dosages for the relevant indication and which together have a more than additive effect.”

• District Court refused to adopt Defendants’ argument that “additive effect” must be proved through a quantitative analysis.
  – Relied on expert opinion that clinicians have reached a consensus that co-administration results in a more than additive effect, indicating synergistic effectiveness.
Claim Construction, Willful Blindness, and Good Faith Belief

Warsaw Orthopedic, Inc. v. NuVasive, Inc., 824 F.3d 1344 (Fed. Cir. 2016)


- Reaffirmed the district court’s judgment of induced infringement by Medtronic Sofamor Danek USA, Inc. (MSD).

- Issue: Whether the jury was presented with substantial evidence that MSD knew or was willfully blind to the fact that it was instructing doctors to infringe the patent.
Claim Construction, Willful Blindness, and Good Faith Belief

Warsaw v. NuVasive

• Claims directed to detecting the presence of and measuring the distance to a nerve during surgery

• “1. A method for assessing the proximity of a spinal nerve relative to a distal end of at least one probe or surgical tool being introduced towards at least one ... region of a patient's spine...comprising:
   — (a) emitting a stimulus signal...;
   — (b) electromyographically monitoring muscles coupled to said spinal nerve...;
   — (c) increasing the intensity level of said stimulus signal until said predetermined neuro-muscular response is elicited by said stimulus pulse and stopping the emission of said stimulus signal immediately after said predetermined neuromuscular response is detected; and
   — (d) communicating to an operator said intensity level of said stimulus signal required to elicit said predetermined neuro-muscular response....”
Warsaw v. NuVasive

- MSD argued it reasonably believed that its NIM-Eclipse device did not infringe.
  - Reasonably construed the stopping limitation narrowly as requiring a complete termination of emission of electrical pulses.
  - When the NIM Eclipse emits a stimulus signal that detects a nerve, it does not stop emission of all electrical signals and instead continues emitting electrical pulses at a lower energy.
Claim Construction, Willful Blindness, and Good Faith Belief

Warsaw v. NuVasive

• Federal Circuit determined that MDS’s position was not supported by the claim language or the prosecution history
  
  — MSD’s theory was inconsistent with its proposed construction of “said stimulus signal”

  — “Given the strength of the evidence NuVasive presented, a reasonable jury could have concluded that MSD must have known that its NIM-Eclipse device ‘stopped’ emitting ‘said stimulus signal’ immediately after that signal elicited a neuromuscular response.”
What About Use Codes?

• Presence of a use code indicates that the listed patent covers an approved indication or use of a drug product.

• A use code is intended to describe the scope of the method of use patent listed in the Orange Book.

• Use codes help identify which indications are patent protected and can be carved out in a section viii certification.

• NDA holder must submit a use code for Orange Book-listed method of use patents.
Use Codes

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U-566: For the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (copd), including chronic bronchitis and emphysema.
A use code should:

- Describe only the specific approved method of use claimed by the patent for which a claim of infringement could reasonably be asserted.

- Identify the section(s) and subsection(s) of the approved labeling that describes the method(s) of use claimed by the patent.

- *Contain adequate detail to assist 505(b)(2) and ANDA applicants in determining whether a listed method of use patent claims a method of use for which the 505(b)(2) or ANDA applicant is not seeking approval.*
Use Codes

FDA’s Guiding Principles

If claimed use is broader than approved indication:
  • Use code must describe only the specific patented method of use described in the label.

If claimed use is narrower than approved indication:
  • Use code must describe only the specific approved method claimed in the patent.

If claimed use is co-extensive with approved indication:
  • Use code must describe only the specific approved method of use claimed by the patent.
Use Codes

Process for Listing Disputes

**Challenge Filed with Statement of Dispute**
- Describes specific grounds for disagreement as to the accuracy or relevance of patent information
- For Use Codes, only a narrative description (NMT 250 words) as to interpretation of patent scope

**NDA Holder Has 30 Days to Respond**
- NDA Holder can:
  - Confirm correctness
  - Amend
  - Withdraw
  - For Use Code, a narrative description (NMT 250 words) as to interpretation of patent scope
  - Signed Verification

**FDA Changes the OB Listing If Requested**
- Only Ministerial
- If NDA Holder confirms correctness, no changes to OB listing
- Otherwise, amended or withdrawn
- A response after 30 days is untimely filed patent information

FINNEGAN

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Use Codes at the Supreme Court


• A generic drug manufacturer may employ the counterclaim provision of the Hatch-Waxman Act to force correction of a use code that inaccurately describes the brand’s patent as covering a particular method of using a drug.
Carve-outs and Use Codes


• BEFORE TRIAL - Teva had carved out the one indication—congestive heart failure—covered by the patent-in-suit from its labeling for its generic copy of Coreg® and argued it did not know its label was inducing infringement.

  – Teva argued that the use code was narrowly focused on CHF only and “that because GSK did not itself believe that the ’000 patent could be asserted against the [other] indication, there is no way Teva could have known that this indication would infringe the patent.”
Carve-outs and Use Codes


  • District court denied motion to dismiss: it was plausible that Teva knew that certain language in the labeling would induce infringement of the CHF patent.
Carve-outs and Use Codes


• AFTER TRIAL - JMOL of no induced infringement

  • District court: no evidence that Teva’s labeling (either skinny or full) caused even a single doctor to prescribe generic carvedilol to a patient to treat mild to severe CHF.

  • “[G]iven the dearth of evidence that doctors read and understand and are affected by labels, and given the vast amount of evidence that doctors’ decisions to prescribe carvedilol during the relevant periods were influenced by multiple non-Teva factors” it was unreasonable for the jury to find induced infringement.
Who Reads the Generic Product Label?

• “A physician would look to the indications and usage section of Defendants’ proposed labels before prescribing everolimus to a transplant patient.”
  • Novartis v. Breckenridge

• “Teva showed that ... doctors ... based their prescription decisions on [various factors] without relying on Teva’s—or any other generic manufacturers’—label.”
  • GSK v. Teva
  • But the court in GSK v. Teva noted that, unlike the typical Hatch-Waxman Act case, GSK’s inducement claims were not premised on a hypothetical, but must instead be supported by sufficient evidence as to what actually happened
Strategic Considerations: Label Language

• Consider drafting labeling to align with patent claim limitations.
  • What can you include?
  • Will an alleged infringer be able to carve it out?
  • Are there sections of the labeling that will support a claim of infringement for all claimed indications?
  • Can you include instructions to help with attribution of all claimed method steps?

• Carefully draft use codes to comply with FDA standards.
  • Marshal support from the entire labeling—not just the indications and usage section—to support the use code.
  • If the use code is challenged, keep infringement in mind when you characterize the scope of the patent.
Induced Infringement

- *Sanofi v. Watson*, 875 F.3d 636 (Fed. Cir. 2017)

- An example of why patent holders should pursue claim language that mirrors an FDA drug label, particularly regarding clinical trials, provide that clinical trial information in a patent application, set forth that clinical trial information in the label, and reference that clinical trial information in the Indications and Usage Section of the label.

- Multaq® is the brand name version of dronedarone, an antiarrhythmic agent directed towards the treatment of heart rhythm problems in patients with atrial fibrillation.

- However, dronedarone also has the risk of doubling mortality rates in patients who have severe heart failure (NYHA Class IV or Class III with a recent hospitalization for heart failure).
History of Multaq® Drug Development

- 1998 - Sanofi files application that established priority date for the ’800 patent on dronedarone composition.
  - Sanofi does not receive FDA approval for Multaq until mid-2009 (leading to the ’167 patent in 2009).

- Between 2001-2003, Sanofi conducts two large-scale clinical trials (EURIDIS and ADONIS) to test effect of dronedarone effect on atrial fibrillation or flutter.
  - Studies show “potential major clinical benefit” of reduced hospitalization or death in patients with currently normal sinus rhythm but had earlier experienced an episode of atrial fibrillation or flutter.
  - Dronedarone further “reduced the incidence of a first recurrence as well as a symptomatic first recurrence within 12 months after randomization, and significantly reduced the ventricular rate during the recurrence of arrhythmia.”
History of Multaq® Drug Development

● In 2002, Sanofi conducts another trial to investigate safety: ANDROMEDA - designed to test the effects of dronedarone on patients with symptomatic heart failure and severe heart failure symptoms.
  ○ Dronedarone actually increased mortality from heart failure.

● European Medicines Agency, upon review, stated that “the clinical relevance needs further consideration...in particular in the context of the negative effects seen in the ANDROMEDA [trials].”

● 2005-2008: Sanofi conducts the large-scale clinical trial, ATHENA, designed to address the potential for clinical benefits of dronedarone that earlier trials had indicated
  ○ ATHENA trial found positive results for dronedarone - led to the filing of the ’167 patent, with four priority documents filed in 2008, two in France and two in the EPO, and also led to FDA approval of Multaq.
Sanofi v. Watson, 875 F.3d 636 (Fed. Cir. 2017)

- Initial ‘167 Application Claim 1 (Filed Apr. 16, 2009):

  1. A method of decreasing the risk of mortality, cardiac hospitalizations, or the combination thereof in a patient, said method comprising administering to said patient an effective amount of dronedarone or a pharmaceutically acceptable salt thereof, with food.

- No reference of clinical trials.
- No indication of any contraindicated symptoms.
- No definition of severe heart failure dangers.
- No description of patient cardiovascular risk factors.

- Such information appeared in issued claims of the ‘167 patent, as seen on the next page, and that information was found in the specification of the ‘167 patent, see, e.g., cols. 3-4, 6, and 14. It was undisputed that issued claims 1 and 8 were entitled to a priority date of February 11, 2009, the second filed French priority application.
Sanofi v. Watson (con’t)

- Final Version of Claim 1 in ’167 Patent: A method of decreasing a risk of cardiovascular hospitalization in a patient, said method comprising administering to said patient an effective amount of dronedarone or a pharmaceutically acceptable salt thereof, twice a day with a morning and an evening meal, wherein said patient does not have severe heart failure, (i) wherein severe heart failure is indicated by: a) NYHA Class IV heart failure or b) hospitalization for heart failure within the last month; and (ii) wherein said patient has a history of, or current, paroxysmal or persistent non-permanent atrial fibrillation or flutter; and (iii) wherein the patient has at least one cardiovascular risk factor selected from the group consisting of:
  I. an age greater than or equal to 75;
  II. hypertension;
  III. diabetes;
  IV. a history of cerebral stroke or of systemic embolism;
  V. a left atrial diameter greater than or equal to 50mm; and
  VI. a left ventricular ejection fraction less than 40%.
Sanofi v. Watson (con’t)

• As will be seen on the following slides, the original label brilliantly referenced in the Indications and Usages section of the label the Clinical Studies of Section 14 of the label that identifies the patients and that has been carried forward into the most recent label.

• Section 14 provided results from the 2005-2008 large scale, pivotal outcome ATHENA clinical study (referenced above), and also the EURIDIS, ADONIS, and ANDROMEDA clinical studies.

• And importantly, the Clinical Studies results, particularly the ATHENA results, were found in the February 9, 2011, French priority document and were carried into the U.S. filing resulting in the ‘167 patent.
Sanofi v. Watson (con’t)

Original Approved Label (07/01/2009):

1 INDICATIONS AND USAGE

MULTAQ® is indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or left ventricular ejection fraction [LVEF] <40%), who are in sinus rhythm or who will be cardioverted [see Clinical Studies (14)].
Sanofi v. Watson (con’t)

Currently Approved Label (03/31/2014):

1 INDICATIONS AND USAGE

MULTAQ® is indicated to reduce the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal or persistent atrial fibrillation (AF) [see Clinical Studies (14)].
Sanofi v. Watson (con’t)

Section 14

14 CLINICAL STUDIES
14.1 ATHENA
14.2 EURIDIS and ADONIS
14.3 ANDROMEDA
14.4 PALLAS

• “The reference to the Clinical Studies section (14) of the label expressly directs the reader to that section for elaboration of the class of patients for whom the drug is indicated to achieve the stated objective, i.e. reduced hospitalization.” Sanofi v. Watson Labs. Inc., 875 F.3d 636, 645 (Fed. Cir. 2017)
  ○ “Section 14 leads with and features a subsection on the ATHENA study, which sets forth the positive results, relating to reduced hospitalization, for patients having the risk factors written into the ’167 patent. And it is only the ATHENA subsection—not any of the three other brief subsections—that identifies a class of patients as having been shown to achieve reduced hospitalization from use of dronedarone...The label thus directs medical providers to information identifying the desired benefit for only patients with the patent-claimed risk factors.” Id.
Sanofi v. Watson (con’t)

- DC: Patents valid and labels induced infringement.
- FC: Affirmed.
  
  - “The label thus directs medical providers to information identifying the desired benefit for only patients with the patent-claimed risk factors.”
  
  - “There was considerable testimony that this label encourages—and would be known by Watson and Sandoz to encourage—administration of the drug to those patients, thereby causing infringement.” The label demonstrate specific intent to encourage physicians to infringe.
  
  - “The content of the label in this case permits the inference of specific intent to encourage the infringing use.”
  
  - Can’t avoid infringement by pointing out that there are substantial non-infringing uses.
Sanofi v. Lupin, 282 F.3d 818 (D. Del. 2017)

- **Multaq®**
  - U.S. Pat. No. 9,107,900 ("the ‘900 patent")
    - Claims 1, 7, 9, and 14

- **Claims at issue in induced infringement assertion:**
  - The “Clinical Studies” section of the label taught that dronedarone could be used for some patients with coronary heart disease, i.e., the ATHENA study.
  - The court found that a POSA would have recognized from the ATHENA study that about 60% of the patients had structural heart disease, and that about half of those patients would have had coronary heart disease. It also found that defendants’ labels suggested that dronedarone could be used in patients in the Age Criteria because the ATHENA study patients ranged from 23-97 years old, where 42% were 75 years old or older.

- Finally, the court held that defendants knew about the ’900 patent and knew their generic dronedarone would be administered in a manner that infringes that patent; they, therefore, intended that result.

- Appealed to Fed. Cir. on Dec. 6, 2017.
  - Feb. 21, 2018 Fed. Circ. issues *vacatur* order after Sanofi v. Watson decision
Sanofi: Why Did It Matter?
Can You Say 10 More Years?

**Patent Data**

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Takeaways from Sanofi

- The “see Clinical Studies” language, included in the FDA drug label, was an extremely important factor that helped Sanofi prove induced infringement in both cases.

- Safety/Efficacy of drug led to specific patient population with patent-claimed risk factors.
  - Consider drafting claims based on a specification reporting results of clinical trials that match those set forth in the label.
  - Avoid waiting too long to file application such that the clinical trial results become prior art against the claims (the results of the ATHENA trials post-dated the critical prior art date).

- Method-of-treatment claims that appear to be very narrow can sound the death knell for generic manufacturers where the claim limitations closely correspond with generic label language, relying in the Indications and Usage section of the label on critical clinical trial results that find their way into the patent specification.

- But see Indications and Usage section of “Labeling for Human Prescription Drugs and Biologicals Products - Content and Format, Draft Guidance for Industry, FDA July 2018, For Comment Purposes Only”
Vanda Pharms. v. West-ward Pharms.

- 887 F.3d 1117 (Fed. Cir. 2018)

- Iloperidone and the CYP2D6 gene
  - Poor metabolizers

- U.S. Reissue Patent 39,198
  - Compound Patent

- U.S. Patent 8,586,610
  - Did not issue until after ANDA filed.
  - A method for treating a patient with iloperidone
    - (1) determining the patient’s genotype by
      - (a) obtaining a biological sample and
      - (b) performing a genotyping assay
    - (2) administering specific dose ranges
Induced Infringement

- Direct Infringement

- Specific Intent

- Proposed label: “The proposed ANDA label is substantially identical in all material respects to the Fanapt® label.”
• West-Ward argument:

  • Proposed label “itself cannot constitute direct infringement of the asserted method claims” and doctor never practiced the asserted claims.

  • Doctor never practiced claims.

  • No evidence of specific intent; no evidence that label encouraged a direct infringer.

  • Non-infringing uses existed.
• West-Ward amended the ANDA by submitting a Paragraph IV certification regarding the '610 patent after that patent issued.

• DC: Granted injunction.

• FC: Affirmed.

• “the proposed label ‘recommends’ that physicians perform the claimed steps,“

• Off-label use is not applicable, and 271(b) does not include “substantial noninfringing use” exception.

• No need to prove actual direct past infringement.

• Patentees in HW litigations asserting method patents do not have to prove that prior use of the NDA-approved drug satisfies the limitations of the asserted claims.
Induced Infringement—“laboratory tests”

Patent Claims
- genotyping tests
  - Experts from both sides testified that the referred-to tests are genotyping tests

Proposed Label
- laboratory tests
  - the label does NOT instruct users to infringe the ‘610 Patent claims

Vanda Pharm.

West-Ward Pharm.

Federal Circuit

No clear error in the district court’s finding that “laboratory tests” are “genotyping tests” and therefore the label induces infringement
Induced Infringement—Obtaining a Biological Sample

Vanda Pharm.

Genotyping tests recommended in the label require obtaining a biological sample

Federal Circuit

No clear error in the district court’s implicit finding that the proposed label recommends obtaining a biological sample and therefore the label induces infringement

Patent Claims

obtaining a biological sample

laboratory tests

Proposed Label

the district court did NOT find that the label recommends obtaining a biological sample

West-Ward Pharm.
Induced Infringement—Non-infringing Uses

West-Ward argued there were substantial non-infringing uses.

Even if not every practitioner will prescribe an infringing dose, that the target dose range “instructs users to perform the patented method” is sufficient to “provide evidence of [West-Ward’s] affirmative intent to induce infringement.”
West-Ward request for rehearing en banc filed June 12, 2018.

Questions posed:


2. Whether proposed label language alone is sufficient to sustain induced infringement under 35 U.S.C. § 271(e)(2)(A) when uncontested objective evidence proves the absence of specific intent.

Arguments:
- Specific intent turns on all record evidence, not just the label language.
- Objective evidence in the record demonstrates a lack of specific intent.
- The new test for induced infringement based solely on label language is wrong and dangerous.
Vanda: Why Did It Matter?
Can You Say 11 More Years?

- The Re 39,198 expired on 11-15-16.
- The ‘610 patent upheld in Vanda expires on 11-02-27!!

### Patent Data

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Drafting and Prosecution:

Keep Enforcement in Mind When Drafting Claims

Consider who will infringe the claims and how infringement will be proven.

Goal: claims that will be directly and literally infringed by competitors.
Consider How Infringement Will Be Proven

Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313 (Fed. Cir. 2003)

• Claim: A having a property which differs from that of A1.

• Specification taught three measurement methods, but failed to limit “which differs” to particular method.

• DC: Invalid and no infringement.
  – Patent failed to identify a single standard by which the “difference” could be measured, so patent invalid for failure to satisfy §112 and no infringement.

• FC: Affirmed because claims indefinite.
  – “One cannot logically determine whether an accused product comes within the bounds of a claim of unascertainable scope.”
Patent Claim Drafting Considerations

Why is the goal to draft claims that will be directly and literally infringed by competitors?

- Avoid difficulties of proving infringement under doctrine of equivalents.

- Deny your competitor the additional defenses to induced and contributory infringement (knowledge, intent, etc.).

- Avoid having to take extensive third party discovery, especially of your own customers or prospective customers.
Drafting and Prosecution Tips

• Coordinate patent, regulatory and clinical personnel early.

• Maintain consistency between claims and likely or actual label language.

• Maintain the coordination referenced above throughout the U.S. patent prosecution and label negotiation with FDA. See Sanofi v. Watson, discussed earlier.
Drafting and Prosecution Tips

- Consider drafting claims so that one party infringes claims (e.g., one party performs all recited steps).

- Consider obtaining a noninfringement opinion to show good-faith belief of noninfringement.

- Opinion of counsel concluding that the patent in question is invalid will not be relevant to induced infringement allegation.

- Consider explicitly pleading indirect infringement and knowledge of the patent prior to the complaint.
Thank You!

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