# Hatch-Waxman Patent Litigation Strategies

**A Lexis Practice Advisor® Practice Note by Jeffrey Alan Hovden, Robins Kaplan LLP**

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This practice note discusses strategies that counsel for brand-name and generic drug companies may employ in pharmaceutical patent litigation under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act. It focuses on litigating infringement and validity of active pharmaceutical ingredient (API), formulation, and treatment patents using court decisions as a guide to what works and what doesn't for each side in Hatch-Waxman litigation.

The terms "brand" and "generic" are used in this practice note as a shorthand to denote a brand-name drug company and a generic drug company respectively. But be aware that in Hatch-Waxman cases, a variety of terms may be used to refer to a generic drug company and a brand-name drug company. The generic drug company may be referred to as the ANDA applicant or the ANDA filer. ANDA is an acronym for Abbreviated New Drug Application, the drug approval application filed by generic drug companies.

A brand-name drug company may be referred to as the innovator, the pioneer, the patent owner, the NDA holder, or the RLD holder. NDA is an acronym for New Drug Application, a type of drug approval application filed by brand-name drug companies. A drug approved based on an NDA is called a reference listed drug or RLD. Also note that while the patent owner and the NDA holder are often the same person, in some cases, they are not. For example, they could be a parent corporation and its licensed subsidiary.

For an explanation of the unique patent litigation scheme under the Hatch-Waxman Act, see Hatch-Waxman Act Fundamentals. If you are new to patent law, you will find an explanation of common patent law terminology and other foundational information in Patent Law Fundamentals Resource Kit. For model forms, specific to Hatch-Waxman litigation, see Patent Infringement Complaint (Hatch-Waxman Act) and Plaintiff's Interrogatories in Hatch-Waxman Patent Litigation (Brand to Generic). For a discussion of pre-litigation considerations, see Hatch-Waxman Pre-suit Considerations from the Generic Perspective and Pre-litigation Preparation and Strategy for Pharmaceutical Product Patents and Exclusivity. For additional information on obviousness as a ground for patent invalidity, see Obviousness in Patent Litigation.

## The Hatch-Waxman Patent Arsenal

The Hatch-Waxman patent arsenal typically comprises three classes of patents: the API patent, the formulation patent, and the treatment (i.e., method of use) patent. These three classes of patents are those that can be listed in the FDA's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, known as the Orange Book.

As explained in Hatch-Waxman Act Fundamentals — The Drug Approval Process under the Act, a Paragraph IV certification that an Orange Book-listed patent is invalid, unenforceable, and/or will not be infringed by the proposed generic drug, is a trigger for patent litigation under the Act. An application for FDA approval of a generic drug that contains a Paragraph IV certification qualifies as an act of patent infringement exposing the generic to an infringement suit by the patent owner and exposing the patent owner to

a counterclaim for a declaration that the patent is invalid, unenforceable, and/or will not be infringed. See 35 U.S.C. § 271(e)(2).

While each class of Orange Book-listed patents contains many variations, the patent litigation issues that are typically raised by each class are as follows:

- **The API patent.** The API patent can cover the active chemical itself, but also the chemical's polymorphs (or pseudopolymorphs and amorphous substances) or optically active forms of the API (enantiomers). To qualify for FDA approval of a generic version of an RLD using the ANDA process, the proposed generic drug must copy the chemical structure of the API used in the RLD. This means that the proposed generic drug will usually infringe an API patent covering the RLD. So, a generic's Paragraph IV certification for an API patent typically asserts only that the patent is invalid.
- **Formulation patents.** Formulation patents are directed to the dosage form and can include, for example, immediate-release or delayed-release dosage forms. For a formulation patent, a generic company can often assert a non-infringement defense based on designing-around the patent claims (sometimes a claim-construction issue), as well as asserting that the patent is invalid and/or unenforceable.
- **Treatment patents.** Treatment patents are directed to methods of use of a drug and may cover particular indications or titration schedules for the drug. (An indication for a drug refers to the use of the drug to treat a particular disease). Sometimes the generic company will be able to specify in its Paragraph IV certification that its proposed generic drug will not infringe the patent because the generic drug will not be sold for the use covered by the patent, but only for another indication for which the RLD has been approved (a so-called Section viii carve-out or "skinny label"). See Hatch-Waxman Act Fundamentals — The Drug Approval Process under the Act.

Be aware that the brand can also assert a patent covering a method of making the API. This type of patent is not listed in the Orange Book. Thus, as counsel for a generic, your due diligence should include conducting an early search for this type of patent so that your client can avoid it by designing an alternative synthesis.

Nothing will guide your Hatch-Waxman litigation strategy so well as actual cases. The following is a discussion of what has worked—and what hasn't—for both the brand and generic side of Hatch-Waxman litigation.

## The API Patent: A Formidable Weapon for the Brand

As noted above, the problem with an API patent is that a generic company using the ANDA process is almost always seeking approval of a generic drug that includes the very API covered by the patent. So, unless there is something about the patent claims that provides an opening for a non-infringement argument (which is rare), the generic must invalidate the patent, or render it unenforceable.

Absent a viable argument that the patent claims are indefinite or not enabled under 35 U.S.C. § 112, the central attack on the validity of the API patent must be based on lack of novelty (anticipation) or obviousness.

But—and this is what makes the API patent so potent—it is unusual for an API patent to be anticipated by something published in the prior art. Of course, as counsel for the generic company, you should still conduct a comprehensive prior art search, especially looking for slip-ups by the brand in which, for instance, the molecule was disclosed in a scientific meeting or in a patent as a small genus of structurally related compounds.

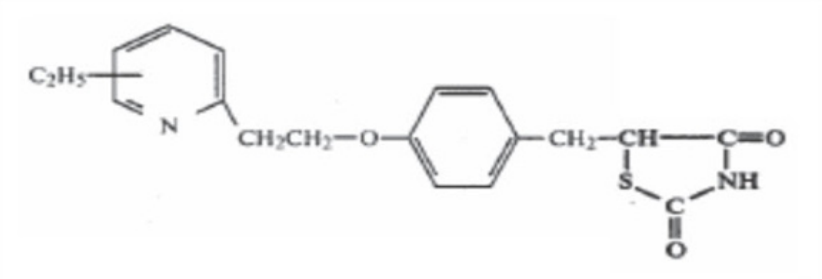
As to obviousness, while it generally became easier to prove obviousness after the Supreme Court's decision in KSR International Co. v. Teleflex, Inc., 550 U.S. 398 (2007), establishing obviousness of drug API patents remains challenging. The Federal Circuit has made it known that the pharmaceutical arts are to be treated as inherently unpredictable. In particular, the Federal Circuit has held that mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection. See Otsuka Pharma. Co., Ltd. v. Sandoz, Inc., 678 F.3d 1280, 1292 (Fed. Cir. 2012). (a lead compound is a chemical compound with known properties, the chemical structure of which a drug company uses as a starting point in drug development).

There is a long line of cases in which the patent examiner rejected API patent claims as prima facie obvious based on structural similarities (so-called structural obviousness). But there is only one significant Hatch-Waxman case in which a court has invalidated an API patent for structural obviousness. This successful challenge is hugely instructive for counsel for both brands and generics. Let's see why this API patent proved vulnerable and compare it to a significant case when an API patent did not. Then we'll look at a case where the Patent Trial and Appeal Board (PTAB) applied these principles to find a patent invalid for structural obviousness. It is of critical importance to both the brand and generic that API patents now seem to have developed an Achilles' heel,

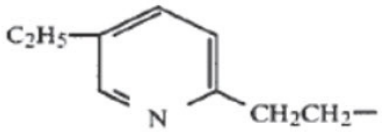
## An API Patent Falls to Obviousness: Comparing the Pioglitazone and Entecavir Cases (or a Tale of Two Cyclics)

Two structural-obviousness cases that look superficially similar had very different outcomes. The first was an unsuccessful challenge to an API patent on the diabetes drug pioglitazone (sold under the brand name Actos®). See Takeda v. Mylan, 417 F. Supp. 2d 341 (S.D.N.Y. 2006), aff'd 492 F.3d 1350 (Fed. Cir. 2007). The second invalidated the API patent for the hepatitis B drug entecavir (sold under the brand name Baraclude®). See BMS v. Teva Pharms., 923 F. Supp. 2d 602 (D. Del. 2013). (Note that while, technically, Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir. 2007) might seem to count as a case that also invalidated an API patent for obviousness, the patent was directed to the besylate salt of the API, rather than the API molecule itself).

In the pioglitazone case, claims 1, 2, and 5 of the asserted API patent were at issue. For the purpose of this discussion, claim 1 is illustrative. It was for a compound with the following formula or a pharmacologically acceptable salt thereof:



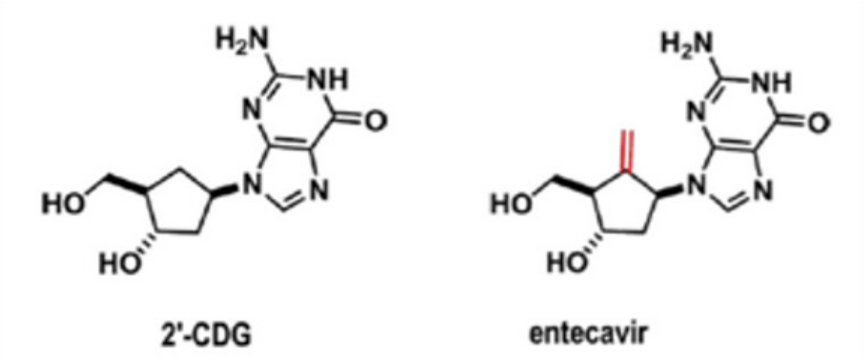

Note that the left-hand C2H5— (ethyl) substituent is hanging out in an indeterminate position. Thus, it can be walked round the pyridine ring and attached at any available position. Ring walking is a straightforward and common approach to drug development, and this reality is reflected in the claim. In claim 2, the ethyl substituent is fixed at the 5 position of the pyridine ring. This is the API, pioglitazone. The following is the formula of claim 2:




An earlier Takeda patent had expressly called out the same basic structure as particularly promising, but instead of 5 ethyl, it had a methyl (CH3—) at the 6 position. In other words, some defendants' argument was that it was obvious to go from (1) the 6 to the 5 position (ring walking, illustrated in claim 1) and (2) a 1-carbon (methyl) substituent to a 2-carbon (ethyl) substituent. This carbon-chain lengthening process, also a common approach in drug development, is called homologisation, with each substituent a homologue of the other. (A homologue here is just a chain of carbons formed by adding or subtracting carbons.)

This case involved complicated issues of adequacy of, and changing of, the defendants' positions, and ended in an award of attorney's fees and costs to the plaintiffs. But the core of the unsuccessful obviousness argument was this: the common drug-development principles of ring walking and homologisation would have motivated and led a person of ordinary skill in the art from the promising 6-methyl prior-art compound to 5-ethyl pioglitazone. The acceptance of this argument—obviousness by application of general principles—may have been controversial. If general principles of drug development could, as a rule, be applied to prior art lead compounds, this could potentially render many API patents invalid for obviousness. As illustrated by this case, structural-obviousness challenges to API patents in Hatch-Waxman cases typically fail.

But compare the pioglitazone case with the entecavir case. Going from the prior art lead compound (left) to entecavir in the '244 patent (right) was held to be obvious:




The court found that this transformation— prior art dihydro 2' -CDG lead compound to methylene-substituted (in red) entacavir—was specifically motivated by a prior-art reference (Madhavan). Entecavir itself was not disclosed in the prior art. But in the structurally similar Madhavan compound, the methylene substitution was found to impart improved properties within the series of antiviral compounds.

It is important not to oversimplify here: a lot of proofs in the case fell into place to support a finding of structural obviousness. The patentee itself had admitted the following:

- Researchers had treated 2'-CDG as a lead compound
- Madhavan disclosed improved properties with the methylene change in other antiviral series
- The addition of carbon at the 5' position was reasonable to a person of ordinary skill in the art

These findings proved prima facie structural obviousness. Indeed, the court indicated that both the excellence of the defendant's expert — and backpedaling of the plaintiff's expert — created a compelling case of prima facie obviousness.

A prima facie showing of obviousness can be rebutted by secondary indicia of non-obviousness such as the commercial success of the invention or the invention's unexpected results. But in the entecavir case, these secondary considerations were weak:

- There was limited commercial success
- The magnitude of the unexpected results (lower toxicity) was comparatively small

On appeal the Federal Circuit affirmed, finding that:

- The 2'-CDG compound was the lead compound (i.e., the natural choice for further development)
- The extracyclic methylene was a minor change taught by the prior art Madhavan reference as significantly superior to the non-methylene molecule in the structurally similar series of compounds

As to the secondary considerations, the appellate court found that sales of the patented drug had been sub-optimal and that any improvement in antiviral properties was an expected difference in degree, not an unexpected difference in kind. Thus, the API patent was invalidated for structural obviousness.

## Ruxolitinib at the PTAB

The PTAB also found structural obviousness in a deuteration case. In a deuterium atom, in addition to the hydrogen/protium atom's proton and electron, there is also a neutron, essentially doubling the mass of the atom and making its bond much stronger than that of the protium atom. Thus, replacement of protium with deuterium may effectively lock down certain metabolic pathways, often to great therapeutic advantage, since metabolic products can be toxic or associated with side effects.

In Incyte Corp. v. Concert Pharms., Inc., IPR2017-01256 (P.T.A.B . Apr. 8, 2019), the PTAB found a deuterated-drug patent — US Pat. No. 9,249,149, entitled Deuterated Derivatives of Ruxolitinib (the '149 patent) — invalid for obviousness. The Board found the '149 patent obvious over the following three prior-art references:

- Rodgers—disclosing and claiming ruxolitinib, and stating that the invention also includes "all isotopes occurring in the . . . final compounds . . . For example, isotopes of hydrogen include tritium and deuterium"
- Shilling—disclosing that ruxolitinib is an orally active and "potent, selective inhibitor of Janus tyrosine kinase 1/2 and the first investigational drug of its class in phase III studies for the treatment of myelofibrosis"
- Concert Backgrounder—disclosing the product platform of CoNCERT Pharmaceuticals, Inc., the potential benefits of deuterium modification, including improved safety, better tolerability, and enhanced efficacy, and stating that "the magnitude and nature of the deuterium benefit cannot be predicted a priori, [so] CoNCERT must test multiple compounds in a range of assays to identify those that are differentiated"

Rejecting the patent owner's core argument that on this record there would have been no reasonable expectation of success selecting ruxolitinib to improve on by deuteration, the Board easily concluded that ruxolitinib qualified as a lead compound. Citing Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1292 (Fed. Cir. 2012), the PTAB noted that the analysis of whether a person of ordinary skill in the art would have chosen the prior art compound as a lead compound is guided by evidence of the compound's pertinent properties, including:

- Positive attributes such as activity and potency
- Adverse effects such as toxicity —and—
- Other relevant characteristics in evidence

Based on its review of the record as a whole, the PTAB determined that the preponderance of the evidence supported finding that a person of ordinary skill in the art would have chosen ruxolitinib as a lead compound. The PTAB noted that it is "the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds," citing Otsuka, 678 F.3d at 1292–93 (quotation marks and citation omitted).

The PTAB agreed with the petitioner that:

- Rodgers expressly claims ruxolitinib and its isomers —and—
- Shilling states that ruxolitinib is "a potent, selective inhibitor of Janus tyrosine kinase1/2 and the first investigational drug of its class in phase III studies for the treatment of myelofibrosis"

Thus, the PTAB found that the Rodgers and Shilling demonstrate useful properties of ruxolitinib that would have led a person of ordinary skill in the art to choose ruxolitinib as a lead compound to make structurally similar compounds (citing Otsuka, 678 F.3d at 1292–93). The PTAB further reasoned that the prior art taught the skilled person where on the molecule to apply deuteration, and why, noting that:

- Shilling taught that oxidative metabolism occurs almost entirely on the cyclopentyl ring of ruxolitinib at Y2 and Y3.
- Concert Backgrounder explained that "deuterium substitution has the potential to create new chemical entities with improved safety, tolerability, and efficacy" and that deuterium compounds useful for this technique are "based on drugs with known efficacy and safety that address clinically validated targets."
- Concert Backgrounder also taught that compounds should be selected that have known "metabolic 'hot spots'" and should be deuterated at some or all of these metabolic hot spots.
- Finally, Concert Backgrounder stated: "At Concert, 'we've never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterated it.'"

The PTAB rejected the patent owner's insistence that the skilled person would have had no expectation of improving the safety and efficacy of ruxolitinib through deuteration, that it was too expensive and that there were tempting alternatives.

The PTAB also implicitly found the connection between the expected improvement in the stability of a drug that had had its metabolic hot spots stabilized by deuteration, and the corollary expectation that a longer half-life of the deuterated drug would mean a lower dose could be used, noting as follows:

> Petitioner and [its expert] further contend that an ordinarily skilled artisan would have expected improved metabolic stability over ruxolitinib based on Shilling and Concert Backgrounder. Petitioner asserts that Shilling's teaching that ruxolitinib metabolism is largely restricted to the cyclopentyl ring would have suggested to a skilled artisan that the compound was an ideal candidate for the deuteration disclosed by the Concert Backgrounder.

> In particular, Concert Backgrounder discloses an example of deuteration with the drug torcetrapib, wherein six of the twelve analogs demonstrated improved metabolic stability. According to [Petitioner's expert], a person of ordinary skill in the art would have expected those six analogs to show enhanced metabolic stability based on known metabolic pathways of torcetrapib.
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> * * *
>
> When that position or "hotspot" is fully deuterated, metabolism is predictably altered. Thus, [Petitioner's expert] considers the deuteration strategy disclosed in the Concert Backgrounder to be somewhat predictable.

The PTAB further noted that the petitioner's expert explained that a reasonable expectation of success would have been recognized by a person of ordinary skill in the art as implicit. This was based on the Concert Backgrounder's statement that deuteration "substantially reduced R&D risk, time, and expense," which is due to the "relative ease and predictability of producing deuterated analogs of known pharmacologically-active compounds and suggests to a POSA a reasonable expectation of success."

### The Takeaway from the Pioglitazone, Entecavir, and Ruxolitinib Decisions

For the patent challenger, the pioglitazone, entecavir, and ruxolitinib cases teach the following:

- While it is not impossible to invalidate an API patent for structural obviousness, it is difficult to do so and you should, if possible, not rely on obviousness as the only ground for patent invalidity.
- Do not rely solely on applying general principles of drug development to a prior art lead compound to establish obviousness.
- In the pharmaceutical arts, it is only a **specific** teaching, motivation, or suggestion in the prior art, directed to very closely related chemical structures, that can be expected to invalidate an API patent for structural obviousness. You should carefully review the prior art for specific teachings on how to modify the lead compound, and closely related compounds.

As the counsel for the patent owner, your central strategic considerations will be to minimize admissions about what is a good lead compound. Early on instruct in-house personnel not to speculate, or talk carelessly or loosely about lead-compound determinations. Carefully vet the prior art to ensure specific disclosures of how to modify the lead compound, and closely related compounds, do not leave the API patent claims vulnerable.

## The Formulation Patent: A Weaker Weapon for the Brand

Unlike API patents, formulation patents may be susceptible to a finding of obviousness based on the application of general principles of design. Notably, excipients (inactive ingredients that act as a medium for active ingredients) are known to have particular properties, and their selection follows somewhat standardized procedures. A good illustration is the zolpidem case discussed below, for which the author was a member of the trial team.

Generics may also be able to avoid infringement of formulation patents by designing around the patent claims. But, depending on how the claims are construed, a design-around that might appear to be sufficient on first glance may ultimately turn out to be inadequate to distinguish the structure of the generic formulation from that of the patent claims. A good cautionary tutorial is the omeprazole case discussed below. (This is also a case for which the author was a member of the trial team).

### The Zolpidem Case

In Purdue Pharm. Prod. L.P. v. Actavis Elizabeth LLC, 2015 U.S. Dist. LEXIS 112253 (D.N.J. Mar. 27, 2015), the patent claims were directed to a sublingual (i.e., absorbed under the tongue), low-dose zolpidem tablet (sold under the brand name Intermezzo®) to treat middle-of-the-night (MOTN) insomnia. The prior art taught full-dose oral (swallow) zolpidem (sold under the brand name Ambien®) to treat a full night's insomnia.

The generics' obviousness argument was essentially as follows:

- Cutting the prior art full night zolpidem dose in half for MOTN insomnia—half an Ambien® for half a night's sleep—is just common sense, and avoids the residual effects with overdosing
- Since a MOTN waker, already in bed and involuntarily awakened, wants an immediate return to sleep—the need for speed—a sublingual formulation is obvious because it has a faster delivery that goes right into the circulatory system, bypassing metabolism through the liver

The central tenet of the patent holder's rebuttal was this: if one awakes MOTN, some sleep deficit has already been paid. So a person of ordinary skill in the art would assume that to return to sleep the patient would need a **higher** zolpidem

dose than the full night dose. But a higher dose is harmful because of its residual sedative effect, leaving an intolerably, even dangerously, groggy commuter behind the wheel of the car heading into work. The patent holder's message was that prior to the patented invention, the problem of treating MOTN sleeplessness thus seemed hopelessly insoluble, so the solution provided by the invention was far from obvious.

Following a bench trial, the court found the patents invalid for obviousness, accepting the generics' commonsense obviousness argument and rejecting the patent holder's rather counterintuitive non-obviousness theory. The Federal Circuit affirmed without opinion.

## The Omeprazole Subcoat Patents Case

In In re Omeprazole Patent Litig., 222 F. Supp. 2d 423 (S.D.N.Y. 2002), the asserted patents were directed to solid dose formulations for the drug omeprazole (a protein pump inhibitor used to treat acid-related conditions such as acid reflux). In particular, the patents were directed to pellets having an acidic enteric coat (to resist stomach acid) with an alkaline (basic) core protecting the API, and a separating layer between the enteric coat and the alkaline core. The separating layer was assumed to halt any interaction between the acidic enteric coat and the alkaline core. The enteric coat assured the pellets a pleasant and intact journey through the harsh environment of the stomach.

To avoid the patented pellet structure, some of the generics designed pellets that had just a core (meant to be non-alkaline) and an enteric coat, but no separating layer. But one generic—KUDCo—designed microtablets that avoided any alkaline reacting compound, thereby meant to omit an alkaline core.

Following a bench trial, the court found that the generics that had tried to avoid the patent claims by omitting a separating layer from their formulations were, in fact, infringing. The court found that only KUDCo did not infringe the patents.

On its face, this result may seem surprising. But the underlying chemistry of the generics' formulation provided the basis for the court's finding of infringement. Even though these generics had deliberately omitted a separating layer, an in situ acid-base separating salt layer formed naturally as a result of an acid-base interaction between the alkaline core and acidic coat. It is Chemistry 101 that the result of an acid-base interaction is a salt. When this interaction occurs all along the interface of the acidic coat and the alkaline core, a salt **layer** forms. That this layer resulted from precisely the acid-base interaction that a separating layer was supposed to prevent did not matter to the court's claim construction and infringement analysis: a separating layer is a separating layer. Thus, all the generics except KUDCo were found to infringe the formulation patents, and were prevented from marketing their generic drugs until the formulation patents had expired.

## The Bendamustine Formulation Case

Recently, accused generics have successfully invalidated formulation patents under the disclosure-dedication doctrine. Under this doctrine, subject matter that is disclosed in the patent specification but not expressly placed in the claims is dedicated to the public. See Claim Drafting: Avoiding Disclosure-Dedication.

In these circumstances the accused generics take advantage of the fact that the classical structure for formulation patents is to explicitly disclose in their specifications huge lists of alternative excipients, such as disintegrants and binders, but then expressly claim only some of the alternatives disclosed in the specification. This classic approach to writing a formulation patent contains a fatal defect: the excipients disclosed in the patent specification as alternatives, but not claimed, are dedicated to the public.

Accordingly, generics that create formulations using unclaimed alternatives are not liable for infringement, either literally or under the doctrine of equivalents. See Eagle Pharms. Inc. v. Slayback Pharma LLC, 958 F.3d 1171 (Fed. Cir. 2020). In *Slayback*, the patent specification for a bendamustine formulation clearly disclosed ethanol as one alternative for the 'pharmaceutically acceptable fluid' claim limitation, but then recited in the patent claims only other such fluids. Thus, a formulation that used ethanol as a pharmaceutically acceptable fluid did not, as a matter of law, infringe the patent claims, either literally or under the doctrine of equivalents. The implications of this jurisprudence are mighty.

## The Takeaway from the Zolpidem, Omeprazole, and Bendamustine Decisions,

For the patent challenger, the zolpidem, omeprazole, and bendamustine cases teach the following:

- **Keep your obviousness argument simple and based on common sense.** In the zolpidem case, the generics' case for obviousness was simple and commonsensical: half a pill for half a night's sleep, under the tongue to provide immediate absorption. In contrast, the patent holder's case seemed counterintuitive: more of the drug is needed for less sleep.
- **Retain an expert with drug formulation experience.** Formulation patents are often susceptible to obviousness challenges, because standard, tried-and-true, and commonsense solutions are generally used and can be well-documented in the prior art. But you need an expert with formulation experience to explain how the formulation choices were well-known, standard options and that—

confronted with the problem at hand—a formulator with an ordinary level of skill would have chosen the patented formulation.

- **Carefully consider the chemistry and claim construction for your non-infringement theory.** Formulation patents, as we've seen, can be designed around. KUDco in the omeprazole case successfully did so. But the other generics were caught off-guard by simple but unanticipated chemistry taking place right under their noses. Thus, even where all seems to be straightforward, it is imperative that all possibilities, under all realistic (or maybe even unrealistic) claim constructions and possible chemical interactions have to be considered.
- **Be vigilant for disclosure-dedication doctrine opportunities.** Formulation patents can provide design-around alternatives to claimed excipients, excipient ratios, and the like by disclosing them in the patent specification but not claiming them. This can provide real low-hanging non-infringement fruit.

As counsel for the patent holder, you should keep in mind the following:

- Formulation patents have a high invalidation rate—at times 70% or so.
- You need an expert who can clearly and credibly explain why a formulation choice that appears simple and obvious is not. Avoid a convoluted or counterintuitive explanation.
- Your testifying expert may need to rely on testing or experiments to establish chemical interactions that may help to establish infringement. But if there is any doubt as to the outcome of the testing or experiments, they should be performed by a separate non-testifying expert before being shared with your testifying expert.
- Beware the resurgent disclosure-dedication doctrine as applied to formulation patents. Work with prosecuting counsel to ensure that all real alternatives are claimed (e.g., in a Markush claim).

# The Treatment Patent

Treatment patents are directed to methods of using a drug. A drug label sets forth how the drug is to be used. For example, it indicates the particular conditions to be treated by the drug and the dosing regimen. Thus, a patent on a method of using a drug to treat the disease that is indicated in the label could be infringed by a person (e.g., a doctor) who uses the drug to treat that disease. In this scenario, the person who uses the drug is the direct infringer. But a drug manufacturer may be held liable for inducing the infringement under 35 U.S.C. § 271(b) if its label for the drug directs that it be used in an infringing manner. The elements of inducement of infringement include proof of direct infringement by a third party and specific intent to encourage a third-party's infringement. See R + L Carriers, Inc. v. DriverTech LLC (In re Bill of Lading Transmission & Processing Sys. Patent Litig.), 681 F.3d 1323 (Fed. Cir. 2012).

But in Hatch-Waxman litigation, typically, the generic drug has not yet been marketed, so there is no actual direct infringement by a third party, and the inducement analysis focuses on the scope of approval sought by the generic company as described in the proposed label for the generic drug. A generic company can avoid a finding of inducement by seeking FDA approval only for a method of use that is not covered by an Orange Book-listed treatment patent (a so-called Section viii carve-out or skinny label). See 21 U.S.C. § 355(j)(2)(A)(viii). This strategy may effectively immunize the generic company from a finding of inducement. This is so notwithstanding the reality that once the generic drug is sold, doctors are free to prescribe it for a use other than that specified in the approved generic drug label (so-called off-label use) and such off-label use may infringe an Orange Book-listed patent.

A generic uses a Section viii carve-out when the brand holds patents on only some of the approved methods of using the drug.

## Infringement: Comparing the Rosuvastatin and Budesonide Cases

If a generic label properly carves-out (i.e., omits) a treatment covered by a treatment patent, there is generally no inducement of infringement. Such was the case for rosuvastatin (sold under the brand-name Crestor®). See AstraZeneca Pharm. LP v. Apotex Corp., 669 F.3d 1370 (Fed. Cir. 2012).

A patented and approved use of rosuvastatin was to treat heterozygous familial hypercholesterolemia (HeFH). An unpatented, but also-approved use, was to treat homozygous familial hypercholesterolemia (HoFH). Because the generic had created a skinny label by carving-out the treatment-patented HeFH indication, leaving in the unpatented HoFH indication, the court held that the generic was not inducing third parties to use its generic product to treat HeFH. This was so even though it is understood that doctors will prescribe the generic drug for all indications that are on the brand's labelling.

A contrasting case is AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042 (Fed. Cir. 2010). A generic tried to avoid a treatment patent directed to a method of treating respiratory diseases by administering a budesonide dose not more than once per day. The brand's label described both once-per-day and twice-per-day dosing. The generic carved-out the once-

per-day dosing, but kept recommendations for starting doses of "0.5 mg total daily dose administered twice daily in divided doses" and was required to keep the FDA-mandated recommendation to titrate down to the lowest effective dose. The court found infringement of the treatment patent, concluding that:

- Starting with a 0.5 mg total daily dose administered twice daily, downward titration would necessarily lead to once-per-day use of the generic's 0.25 mg vial of budesonide
- The generic's label would inevitably lead some users to practice the claimed treatment of once-daily administration of the drug

## Invalidating Treatment Patents: The Omeprazole Case

A patent claim is invalid for lack of novelty (i.e., anticipation) if a single prior art reference discloses each claim limitation, either expressly or inherently. One way in which treatment patents have been successfully invalidated is by showing that the use of the API in the prior art inherently treated patients according to the treatment patent, even though at the time this wasn't recognized. A patent directed to a previously unknown mechanism of action for an API is vulnerable to such a finding of anticipation. For an example, we return to the omeprazole case. In re Omeprazole Patent Litig., 222 F. Supp. 2d 423 (S.D.N.Y. 2002).

Treatment of ulcers by omeprazole was disclosed in the prior art. Subsequently, it was found that ulcers were associated with *H. pylori* infection, not burns in the stomach lining from spicy food, as had been the conventional wisdom. Treatment of ulcerative *H. pylori* infection by omeprazole was then patented. But the *H. pylori* treatment patent claims were found invalid for anticipation: because the prior art showed treatment of ulcers by omeprazole, and because those ulcers had harbored *H. pylori* infections, then—though unrecognized at the time—omeprazole had inherently treated the *H. pylori* infections.

## The Takeaway from the Rosuvastatin, Budesonide, and Omeprazole Decisions

As counsel for a generic company, keep the following in mind when litigating treatment patents:

- A Section viii carve-out is an effective shield against a finding of infringement of a treatment patent, notwithstanding the fact that once the generic drug is on the market, doctors will prescribe it for all indications that are on the brand's labelling, including a patented treatment
- But courts will look past mere labelling verbiage to see if the generic's label indication really would lead third parties to infringe the treatment patent
- For a Section viii carve-out to be effective, you must ensure that the generic's labelling does not either expressly or inherently point the way for third parties to practice the treatment claims
- You should scrutinize the prior art for old uses of the drug because if the patented treatment is inherent in the prior art use, the treatment claims may be invalidated for anticipation

As counsel for the patent holder, you should do the following:

- Try to ensure that the patent claims are drafted so as to avoid reference to an old mechanism of use (i.e., a mechanism of action for the drug disclosed either expressly or inherently (e.g., *H. pylori* infection) in a prior art reference
- Notwithstanding a Section viii carve-out, carefully examine the generic's label for any argument that the labelling statements would inherently induce third parties to practice the treatment claims (See, e.g., GlaxoSmithKline LLC v. Teva Pharms. USA, Inc., 2016 U.S. Dist. LEXIS 94438 (D. Del. Jul. 20, 2016), where summary judgment for the defendant was denied because the carved-out use—decreased mortality due to congestive heart failure—may overlap with the use left in the generic label—treatment of post-myocardial infarction left ventricular dissynchrony).

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Jeff practices in the area of patent litigation, with a focus on generic pharmaceutical patent cases under the Hatch-Waxman Act and within the biotechnology industry. He has litigated numerous patent infringement and invalidity actions, including many cases involving top-selling worldwide prescription drugs for both generic and name-brand clients.

Jeff routinely advises clients on their intellectual property portfolios and has extensive experience with the Food, Drug, and Cosmetic Act's drug-approval provisions and their attendant regulations. He also provides infringement, validity, and due diligence opinions.

In addition to patents, Jeff is experienced with copyrights, particularly those involving functional works and counsels biotechnology clients regarding licensing matters.