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Takeaways From Fed. Circ. Hatch-Waxman IPR Case

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January 17, 2019, 4:56 PM EST


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On Jan. 11, 2019, the U.S. Court of Appeals for the Federal Circuit issued a precedential opinion in Amerigen Pharmaceuticals Ltd. v. UCB Pharma GmbH[1] affirming the decision of the Patent Trial and Appeal Board in an inter partes review proceeding finding that a pharmaceutical patent directed to "prodrug" compounds was not unpatentable as obvious.

Amerigen filed an IPR petition against UCB asserting that certain claims of UCB's U.S. Patent 6,858,650 were unpatentable as obvious. The '650 patent covers the compound fesoterodine, the active ingredient of the brand product Toviaz, which is prodrug of a previously known active compound, 5-HMT. The PTAB ruled in UCB's favor, finding that Amerigen failed to prove obviousness of claims directed to fesoterodine. Amerigen also failed to prevail in a related Hatch-Waxman district court action involving Amerigen's abbreviated new drug application for a generic version of Toviaz, resulting in Amerigen's Paragraph III certification that it would not seek final U.S. Food and Drug Administration approval until after expiration of the '650 patent in 2022.

On appeal of the PTAB's decision to the Federal Circuit, the court ruled that, despite its Paragraph III certification, Amerigen had sufficient Article III standing to appeal from the PTAB. On the merits, however, the Federal Circuit affirmed the PTAB's decision, finding that Amerigen had failed to show a prior art motivation to make a prodrug of 5-HMT, or any motivation to make the specific chemical modifications leading to fesoterodine.

This ruling provides an informative data point regarding standing for Federal Circuit appeals from the PTAB in the Hatch-Waxman context, as well as considerations for brand companies facing obviousness challenges to patents claiming prodrug compounds.

Hatch-Waxman and Inter Partes Reviews

Under the Hatch-Waxman Act, a generic drug manufacturer submitting an ANDA to the FDA for a generic version of a branded product must certify, as to each patent listed in the FDA's "Orange Book" for the branded product, whether the patent has expired (Paragraph II certification), the date on which the patent will expire (Paragraph III certification), or that the patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (Paragraph IV certification).[2] Under 35 U.S.C. § 271(e)(2)(A), a branded drug manufacturer may bring an early patent infringement suit in federal district court against an ANDA applicant seeking approval for a drug "claimed in a patent or the use of which is claimed in a patent before the expiration of such patent" — typically, following notice of the applicant's Paragraph IV certification. If, following such a suit, the generic drug manufacturer is found to infringe an Orange Book listed patent in a final decision from which no appeal can be or has been taken, the generic must amend its ANDA to include a Paragraph III certification with respect to the patent at issue[3] — in which case, the FDA will not approve the ANDA until the expiration of that patent.[4]

In addition to Hatch-Waxman litigation in federal district courts, ANDA applicants may challenge the patentability of Orange Book-listed patents in IPR petitions before the PTAB. The PTAB is an administrative entity, and has broad statutory jurisdiction to hear IPR petitions from any person other than the patent owner.[5] IPR petitioners also have a statutory right to appeal the PTAB's denial of a petition to the Federal Circuit[6] — but in order to do so, the petitioner must meet the requirements for standing under Article III of the U.S. Constitution, including showing that the appellant has "(1) suffered an injury in fact, (2) that is fairly traceable to the challenged conduct of the appellee, (3) that is likely to be redressed by a favorable judicial decision."[7]

The '650 Patent and the PTAB Decision Below

UCB owns the '650 patent, which covers a compound called "fesoterodine." Fesoterodine is an antimuscarinic drug marketed as Toviaz to treat urinary incontinence. UCB listed the '650 patent, among other patents, in the FDA's "Orange Book" for Toviaz. Fesoterodine is "prodrug," meaning that, unlike typical drugs, fesoterodine "is an inactive molecule as-delivered," and "requires transformation within the body into its active therapeutic form" — the compound "5-HMT."[8] The '650 patent is listed in the Orange Book as expiring on July 3, 2022.

Amerigen filed an ANDA for a generic version of Toviaz, which originally contained a Paragraph IV certification to the '650 patent.[9] Following judgment against Amerigen in a related Hatch-Waxman district court litigation that the '650 patent was infringed and not invalid, Amerigen amended its ANDA to include a Paragraph III certification to the '650 patent.[10] Amerigen's ANDA is "tentatively approved" by the FDA — but in view of Amerigen's Paragraph III certification, the FDA cannot grant Amerigen final approval until the expiration of the '650 patent.[11]

In the IPR proceeding below, the PTAB denied Amerigen's petition, finding that Amerigen failed to prove that the '650 patent claims to fesoterodine would have been obvious.[12] Amerigen's IPR petition relied

on (1) references disclosing 5-HMT — the active metabolite of the ’650 patent compound fesoterodine — as a pharmacologically active metabolite of the earlier drug tolterodine; (2) references describing prodrug design principles in general; and (3) references regarding pharmaceutical salts.[13] The PTAB found that a person of ordinary skill in the art would have chosen 5-HMT as a lead compound for further development, to address some concerns about the inconsistent metabolism of the earlier compound tolterodine.[14] The PTAB further found, however, that a person of skill would not have been motivated to modify 5-HMT into a prodrug compound; and that even if a person of skill were so motivated, the prior art would not have motivated them to make the specific chemical modifications that would lead to the patented compound fesoterodine. Amerigen appealed; and in response, UCB moved to dismiss the appeal for lack of Article III standing.[15]

The Federal Circuit’s Opinion Regarding Article III Standing

The Federal Circuit ruled for Amerigen on the issue of Amerigen’s standing to appeal. Despite Amerigen’s Paragraph III certification precluding it from marketing an infringing generic product during the lifespan of UCB’s ’650 patent, the Federal Circuit nonetheless found that Amerigen had proven a cognizable injury that was traceable to UCB, and that would be redressed by an appellate ruling in Amerigen’s favor.[16]

With regard to the justiciable dispute, the Federal Circuit agreed with Amerigen’s contention that it had a justiciable dispute because the ’650 patent, and its listing in the Orange Book, was blocking the launch of Amerigen’s ANDA product.[17] In the panel’s view, if the Federal Circuit were to determine that the ’650 patent was unpatentable, the NDA holder for Toviaz would be required to notify the FDA, which in turn could result in the FDA “delisting” the ’650 patent from the Orange Book[18] — enabling Amerigen to convert its “tentative approval” to a final ANDA approval and launch prior to the expiration of the ’650 patent.[19] The court also held that this alleged injury was fairly traceable to UCB, who submitted the ’650 patent for listing in the Orange Book.[20]

While the court noted that Amerigen’s Paragraph III status might deprive it of standing in the context of a Hatch-Waxman infringement action, the court found that the standing considerations for an appeal from an IPR decision under the America Invents Act are broader, and could be satisfied by injury alleged by Amerigen in this case.[21] The Federal Circuit relied on its prior decision in Apotex Inc. v. Daiichi Sankyo Inc.[22] for the proposition that “listing a patent in the Orange Book may create a cognizable injury independent of the prospect of infringement liability.”[23]

The Federal Circuit’s Opinion Upholding Nonobviousness of a Prodrug Compound Patent

On the merits of the PTAB’s decision, the Federal Circuit sided with UCB, affirming the PTAB’s decision that the ’650 patent claims to fesoterodine were not unpatentable as obvious. Applying a “lead compound” analysis framework,[24] the panel found that substantial evidence supported the PTAB’s findings that a person of ordinary skill would not have been motivated to make any prodrug modifications of the lead compound “5-HMT,” let alone the specific chemical modifications leading to the claimed compound fesoterodine.

The Federal Circuit rejected Amerigen's broad assertion that it was generally obvious to make prodrugs of compounds for purposes of improving bioavailability. The court credited the PTAB's findings that the potential benefits of making a prodrug were offset by the substantial complexity of developing prodrug compounds — which are new chemical compounds and thus require an evaluation of "toxicity, bioavailability, receptor affinity, pharmacokinetics, and pharmacodynamics" that could not be predicted a priori.[25] In the case of 5-HMT in particular, the court credited the finding below that a person of skill would not have been sufficiently concerned about the bioavailability or "lipophilicity" of that compound to undertake the substantial risk of making a new, unpredictable prodrug compound.[26]

The Federal Circuit further credited the PTAB's findings that, even if a skilled artisan were to consider making a prodrug of 5-HMT, they would not have been motivated to make the specific chemical modifications leading to the claimed compound fesoterodine. [27] Specifically, the court found there was substantial evidence that (1) it could not have been known whether fesoterodine or other esters of 5-HMT would be "inactive" prodrug compounds; (2) there were no prodrugs of compounds analogous to 5-HMT that might have suggested how to proceed; (3) the art described many options for different possible prodrug approaches, and there was no particular reason to select an "ester" approach as used in fesoterodine; and (4) even with an "ester" approach, there were many possible variants that could have been made, and no motivation to make the specific ester at the specific position used for fesoterodine.[28]

Analysis and Implications

While the Federal Circuit's decisions on standing issues frequently turn on the specific facts of the case, the Amerigen opinion provides an informative data point regarding how the court may approach the standing of generic manufacturers to bring IPR appeals in the Hatch-Waxman litigation context. In Amerigen, the court found that an ANDA applicant had standing to appeal an adverse IPR decision — even though the applicant maintained a Paragraph III certification to the patent at issue — in view of the possible "delisting" of that patent following a Federal Circuit decision in the ANDA applicant's favor. In doing so, the court looked beyond its precedent regarding standing in IPR appeals, and relied on case law regarding declaratory judgment standing to trigger "forfeiture" of a first-filer's 180-day exclusivity period. Notably, the ANDA applicant in this case had tentative approval from the FDA, and future Federal Circuit panels may reach different conclusions under different sets of facts, such as an ANDA that has not yet received tentative approval.

The Amerigen opinion also illustrates important considerations for brand companies in protecting prodrug patent claims from invalidity challenges alleging that prodrug compounds would have been obvious to design and develop. As the Federal Circuit recognized, the development of prodrug compounds implicates a complex set of chemical and biological problems — particularly where, as in this case, there were many possible options of potential prodrug compounds to make, and little guidance to predict or even suggest what approach, if any, would work. Where, as in the Amerigen opinion, there was not a clear motivation in the prior art to undertake development of a prodrug from a

lead compound in the first instance, this case illustrates how the challenges and complexity of prodrug development can outweigh a general assertion that a prodrug compound might be beneficial.

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[1] See Amerigen Pharms. Ltd. v. UCB Pharma GmbH, No. 2017-2596 (Fed. Cir. Jan. 11, 2019).

[2] 21 U.S.C. § 355(j)(2)(A)(vii).

[3] 21 C.F.R. 314.94(a)(12)(vii)(A).

[4] 21 U.S.C. § 355(j)(5)(B)(ii)

[5] 35 U.S.C. § 311.

[6] 35 U.S.C. § 319.

[7] Phigenix, Inc. v. Immunogen, Inc., 845 F.3d 1168 (Fed. Cir. 2017).

[8] Amerigen Opinion at 2.

[9] Id. at n. 13.

[10] Id.

[11]Id. at 11-12.

[12] Id. at 6-7.

[13] Id. at 4-6.

[14] Id. at 6.

[15] Id. at 9. The Federal Circuit denied UCB's standing motion without prejudice, to be resolved following consideration of the merits. See id.

[16] Id. at 10-16.

[17] Id. at 11-13.

[18] Id.

[19] Id. Additionally, the Federal Circuit explained that the record was "unclear" whether another generic manufacturer would be entitled to 180-day exclusivity – but noted that the even if that was the case, Amerigen would still be able to "launch its competing product substantially earlier than it otherwise could upon the patent's expiration." Id. at 13.

[20] Id. at 16.

[21] Id. at 15-16.

[22] Apotex, Inc. v. Daiichi Sankyo, Inc., 781 F.3d 1356, 1359–61 (Fed. Cir. 2015). The court distinguished its prior decision in Janssen Pharms., N.V. v. Apotex, Inc., 540 F.3d 1353 (Fed. Cir. 2008) – which found that that "the inability of the later filing generic company 'to promptly launch its generic [product] because of [the first filer's] 180–day exclusivity period is not a cognizable Article III controversy'" – on the grounds that, under the "pre-MMA" law controlling in Janssen, a decision on the merits in favor of the generic in that case would not have given them an express path to market.

[23] Amerigen Opinion at 13-14.

[24] See, e.g., id. at 23 (citing Takeda Chem. Indus., Ltd. v. Alapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007)).

[25] Id. at 19-20.

[26] Id. at 18-19.

[27] Id. at 20.

[28] Id. at 20-22.