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UNPREDICTABILITY OF THE ART AND THE ROLE OF EFFICACY DATA IN PATENT VALIDITY CHALLENGES

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In *OSI Pharmaceuticals, LLC v. Apotex Inc.*,[1] the Federal Circuit reversed a decision of the Patent Trial and Appeal Board ("PTAB") that had found four method of treatment claims unpatentable as obvious. The Federal Circuit concluded that the PTAB's factual finding was not supported by substantial evidence—that one skilled in the art would have had no reasonable expectation of success to achieve the claimed invention when looking at the prior art of record. The decision is noteworthy because the court implied that the prior art would need treatment efficacy data in order to render these method of treatment claims obvious. This holding has the potential to implicate a requirement of efficacy data for other invalidity arguments, namely anticipation[2] or lack of enablement.[3]

Apotex petitioned for an *inter partes* review ("IPR") of claims 44–46 and 53 of U.S. Patent No. 6,900,221 ("the '221 patent") using three pieces of prior art.[4] The claims are directed to a method for treating several cancers in a mammal by administering a specific chemical compound.[5] Claim 53 is limited to treatment of non-small cell lung cancer ("NSCLC").[6] The claimed compound, called erlotinib, gained FDA approval in 2004 for treatment of patients with types of metastatic NSCLC.[7] As mentioned by the Federal Circuit, many proposed therapies for NSCLC did not show treatment efficacy during clinical trials and very few gained FDA approval.[8] Since erlotinib's approval, the '221 patent has been the subject of district court litigations,[9] including current litigation where OSI asserted the patent against Apotex for Apotex's generic drug application.[10]

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1. 939 F.3d 1375 (Fed. Cir. 2019).

2. Patent claims can be challenged in district court litigation and in IPR as being anticipated by the prior art, and thus not meeting the statutory novelty requirement under 35 U.S.C. § 102. 35 U.S.C. §§ 282(b)(2); 331(a).

3. Patent claims can be challenged in district court litigation as failing to enable one skilled in the art to make or use the claimed invention, and thus not meeting the statutory enablement requirement under 35 U.S.C. § 112. 35 U.S.C. § 282(b)(3).

4. Apotex Inc. v. OSI Pharm. LLC, No. IPR2016-01284, 2018 WL 335096, at *1 (P.T.A.B. Jan. 8, 2018).

5. '221 patent at 35:26–36.

6. '221 patent at 35:64–65. Claim 45 adds an adjuvant to the treatment, and in claim 46 the treatment comprises additional activity. '221 patent at 35:37–42.

7. *OSI Pharm.*, 939 F.3d at 1378; Astellas Pharma US, Inc. & Genentech, Inc., Tarceva Prescribing Information 1 (Oct. 2016). OSI markets erlotinib under the branded name "Tarceva." *OSI Pharm.*, 939 F.3d at 1378.

8. *OSI Pharm.*, 939 F.3d at 1378.

9. *Apotex*, No. IPR2016-01284, 2018 WL 335096, at *1.

10. Complaint at ¶ 1, OSI Pharm., LLC. et al. v. Apotex Inc. et al., No. 1:15–cv–00772, (D. Del. Sept. 2, 2015).

In its final written decision, the PTAB concluded that the four challenged patent claims were invalid because they would have been obvious to one skilled in the art.[11] The PTAB first construed "therapeutically effective amount" as an "amount sufficient to treat the mammal" of the claim, which did not require administration of a clinically effective amount of erlotinib to a human.[12] The PTAB analyzed the three pieces of prior art provided by Apotex—Schnur,[13] Gibbs,[14] and OSI's 10-K[15]—under this construction. The PTAB found that Schnur disclosed all elements of challenged claims 44 and 53, except the treatment of NSCLC.[16] And, according to the PTAB, Gibbs and OSI's 10–K both "explicitly suggest[ed]" treatment of NSCLC with erlotinib.[17] Ultimately, the PTAB concluded that the combinations of Schnur with Gibbs and Schnur with OSI's 10-K "would have provided a person of ordinary skill with a reasonable expectation of success in using erlotinib to treat NSCLC in a mammal."[18] The PTAB specifically noted that proof of clinical efficacy in human NSCLC patients was not required to demonstrate obviousness.[19] OSI appealed the PTAB's decision to the Federal Circuit, arguing that the PTAB's factual finding of a reasonable expectation of success was not supported by substantial evidence.[20]

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11. *OSI Pharm.*, 939 F.3d at 1381 (citing *Apotex*, No. IPR2016-01284, 2018 WL 335096, at *11).

12. Final Written Decision at 8, Apotex Inc. v. OSI Pharm. LLC, No. IPR2016-01284 (P.T.A.B. Jan. 8, 2018). [The Westlaw version of this decision has incorrectly assembled the text of this section.] As defined in the specification, "treating" was agreed as referring to "reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition." '221 patent at 14:9–13.

13. U.S. Patent No. 5,747,498 to Schnur ("Schnur"). Schnur discloses compounds, including erlotinib, with similar function and are useful for treatment of a variety of cancers. *OSI Pharm.*, 939 F.3d at 1379 (citing Schnur).

14. Jackson B. Gibbs, *Anticancer Drug Targets: Growth Factors and Growth Factor Signaling*, 105 J. CLINICAL INVESTIGATION 9, 9–13 (2000) ("Gibbs"). Gibbs is a review paper that summarizes other studies on cell signaling mechanisms and their association with cancer, including one on erlotinib. *OSI Pharm.*, 939 F.3d at 1380 (citing Gibbs).

15. OSI Pharmaceuticals, Inc., Annual Report (Form 10-K) (Sept. 30, 1998) ("OSI's 10-K"). OSI's 10-K SEC filing includes a statement about clinical trials involving erlotinib for a variety of cancers. *OSI Pharm.*, 939 F.3d at 1380–81 (citing OSI's 10-K).

16. *Apotex*, No. IPR2016-01284, 2018 WL 335096, at *11.

17. *Id.* at *15.

18. *OSI Pharm.*, 939 F.3d at 1382 (citing *Apotex*, No. IPR2016-01284, 2018 WL 335096, at *22).

19. *Apotex*, No. IPR2016-01284, 2018 WL 335096 at *15.

20. *OSI Pharm.*, 939 F.3d at 1382. OSI also challenged the constitutionality of IPRs applied to patents issued before the America Invents Act. *Id.* at 1382, 1386. OSI later conceded that the Federal Circuit's more recent decisions foreclosed the issue. *Id.* at 1386 (citing Celgene Corp. v. Peter, 931 F.3d 1342, 1362 (Fed. Cir. 2019) and Arthrex, Inc. v. Smith & Nephew, Inc., 935 F.3d 1319, 1331 (Fed. Cir. 2019)). For commentary on *Celgene Corp. v. Peter*, *see* Will Czaplyski, Comment, *Federal Circuit Takes on Takings Concerns for Inter Partes Review of Pre-AIA Patents*, HARV. J.L. & TECH. DIG. (2019), https://jolt.law.harvard.edu/digest/inter-partes-review-pre-aia.

Writing for the unanimous panel, Judge Stoll reversed the PTAB's finding of obviousness. First, the court concluded that the PTAB misinterpreted the asserted prior art.[21] In analyzing Gibbs, a scientific review article, the court looked to Gibbs's cited references and found they did not disclose treatment of NSCLC using erlotinib.[22] Similarly, the court found that OSI's 10-K did not disclose preclinical efficacy data specific for NSCLC.[23] Thus, the court stated that the asserted prior art did not disclose any data — human, animal, or in vitro — on the efficacy of erlotinib in treating NSCLC.[24] Second, the court concluded that, when "properly read," the combinations of prior art did not provide substantial evidence to support a reasonable expectation of success.[25] In reaching this conclusion, the court credited evidence of the unpredictability and high failure rate of NSCLC treatments in clinical trials.[26] Taken together, the court stated that Schnur, Gibbs, and OSI's 10-K provided "no more than hope—and hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success in a highly unpredictable art such as this."[27] However, the court did limit its holding, stating that efficacy data would not always be required to show a reasonable expectation of success.[28]

The Federal Circuit's jurisprudence on method of treatment patent claims has attracted recent attention on its analysis of patentable subject matter.[29] *OSI Pharmaceuticals* is another decision that could affect analysis of drug method of treatment claims, particularly in fields of art that are considered especially unpredictable. However, it is not clear how broadly or narrowly courts will construe the requirement for efficacy data in an obviousness analysis. Nor is it clear if the decision in *OSI*

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21. *OSI Pharm.*, 939 F.3d at 1382–83. For PTAB decisions, the Federal Circuit reviews legal conclusions de novo and findings of fact for substantial evidence. *Id.* at 1381.

22. *Id.* at 1383. The court also relied on testimony from Apotex's expert witness and a declaration by Gibbs's author. *Id.* at 1383–84.

23. *Id.* at 1385.

24. *Id.* at 1383.

25. *Id.* at 1384.

26. *Id.* at 1383, 1384.

27. *Id.* at 1385. The court stated that "given a 99.5% failure rate and no efficacy data or any other reliable indicator of success, the only reasonable expectation at the time of the invention was failure, not success." *Id.*

28. *Id.* ("To be clear, we do not hold today that efficacy data is always required for a reasonable expectation of success. Nor are we requiring 'absolute predictability of success.' We conclude only that, on these particular facts, a reasonable fact finder could not find a reasonable expectation of success.") (citation removed).

29. In August 2019, the court issued a nonprecedential opinion concluding that a method of treatment patent was invalid under § 101. INO Therapeutics LLC v. Praxair Distribution Inc., No. 2018-1019, 2019 WL 4023576 (Fed. Cir. Aug. 27, 2019) (nonprecedential decision). For a commentary on this decision, *see* Irene Hwang, Comment, *Federal Circuit Disagrees on Alice/Mayo Application to Medical Treatment Patents*, HARV. J.L. & TECH. DIG. (2019), https://jolt.law.harvard.edu/digest/alice-mayo- application-medical-treatment.

Pharmaceuticals will affect analyses of other statutory requirements. This comment will explore the potential effects of the decision on analyses of lack of enablement and anticipation.

One question is whether efficacy data would be required to show enablement of similar method of treatment claims. A patent specification must provide sufficient teaching so one skilled in the art can make and use the claimed invention.[30] This requirement can be satisfied if the invention can be practiced without undue experimentation, in light of eight factors, one of which is the predictability or unpredictability of the art.[31] When the field is more unpredictable, more detail in the specification would be necessary to enable the claims.[32] In *OSI Pharmaceuticals*, the court found that with the high level of unpredictability for NSCLC treatment, a more detailed disclosure in the prior art was required in order to show obviousness. Thus, a patent holder may need to admit unpredictability in the art to overcome an obviousness argument, which would create a higher evidentiary bar to demonstrate enablement. A district court litigation could include both enablement and obviousness challenges, requiring the parties to navigate their positions carefully.[33] For example, a patent owner may not be able to successfully rely on prior art that did not render a claim obvious in order to support enablement of the claim.[34] If efficacy data in the prior art were required to show obviousness, there is a strong argument that efficacy data would be required in the patent specification in order to enable the same method of treatment claims.

Another question is whether prior art would need to disclose efficacy data to anticipate similar method of treatment claims. In order to anticipate a patent claim, a reference needs to be enabling so one skilled in the art can make the invention without undue experimentation.[35] But

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30. 35 U.S.C. § 112.

31. The eight factors to be considered in determining undue experimentation under the enablement requirement are "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

32. *In re* Fisher, 427 F.2d 833, 839 (C.C.P.A. 1970) ("In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.").

33. Roy D. Gross, *Harmonizing the Doctrines of Enablement and Obviousness in Patent Litigation*, 12 U. PITT. J. TECH. L. POL'Y 1, 10–15 (2012) (describing the inherent difficulties faced by litigators in advancing invalidity arguments of both obviousness and lack of enablement).

34. *In re* '318 Patent Infringement Litig., 578 F. Supp. 2d 711, 736 (D. Del. 2008), *aff'd*, 583 F.3d 1317 (Fed. Cir. 2009) ("[S]ince plaintiffs rely exclusively on the prior art to establish enablement, the court agrees with defendants that the '318 patent cannot both be non-obvious and enabled.").

35. American Calcar, Inc. v. American Honda Motor Co., Inc., 651 F.3d 1318, 1341 (Fed. Cir. 2011) ("To be anticipatory, a reference must describe, either expressly or inherently, each

according to the Federal Circuit, efficacy is not required for such a disclosure to be enabling.[36] Now, the case law suggests there could be a higher standard for prior art disclosures in obviousness analyses than in anticipation analyses; efficacy data in the prior art could be required to show obviousness, whereas efficacy data in the prior art may not be required to show anticipation of the same claims. This difference could be justified as a scale balancing the number of pieces of prior art to disclose the invention and the specificity of the disclosures. Alternatively, the decision in *OSI Pharmaceuticals* could indicate the existence of certain unpredictable fields where efficacy data would be necessary in order to anticipate claims as well as make them obvious.

Currently there is room to argue that these three invalidity analyses should be developed in parallel, or to argue that the efficacy data requirement should be limited to obviousness under a specific set of facts. Importantly, the different analyses do require different breadth of disclosure. The full scope of the patent claim must be enabled, whereas disclosure of any embodiment falling under the claim can support a finding of anticipation or obviousness.[37] This suggests that efficacy data requirements under the different analyses may not completely overlap. The challenges involving the '221 patent between OSI and Apotex will likely not address how the *OSI Pharmaceuticals* holding on obviousness interacts with requirements for demonstrating enablement and lack of anticipation. The PTAB declined to institute IPR based on anticipation, so anticipation and obvious arguments were not advanced simultaneously.[38] Further, the parties agreed during the district court litigation that the invalidity arguments would be limited to those in the IPR, meaning no anticipation or lack of enablement arguments would be made by the defendants during litigation.[39] As a result, future litigations and IPR challenges will be needed to determine how far the efficacy data requirement extends.

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and every claim limitation and enable one of skill in the art to practice an embodiment of the claimed invention without undue experimentation.").

36. Impax Labs. Inc. v. Aventis Pharm. Inc., 468 F.3d 1366, 1383 (Fed. Cir. 2006) ("[P]roof of efficacy is not required for a prior art reference to be enabling for purposes of anticipation." (citing Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1326 (Fed. Cir. 2005))).

37. Timothy R. Holbrook, *Patent Anticipation and Obviousness as Possession*, 65 EMORY L.J. 987, 1037–38 (2016) (describing differences in enablement, obviousness, and anticipation and arguing for a more unified theory of the patent requirements).

38. Institution Decision at 8, Apotex Inc. v. OSI Pharm. LLC, No. IPR2016-01284 (P.T.A.B. Jan. 9, 2017).

39. Stipulated Order at ¶ 5, OSI Pharm. LLC. et al. v. Apotex Inc. et al., No. 1:15–cv–00772 (D. Del. Jan. 25, 2017).