United States Court of Appeals for the Federal Circuit

05-1313

IMPAX LABORATORIES, INC.,

Plaintiff-Appellant,

v.

AVENTIS PHARMACEUTICALS INC.,

Defendant-Appellee.

C. Kyle Musgrove, Kenyon & Kenyon, of Washington, DC, argued for plaintiff-appellant. With him on the brief were Philip J. McCabe, of San Jose, California; Michael M. Shen, of Washington, DC; and Steven J. Lee, of New York, New York .

Paul H. Berghoff, McDonnell, Boehnen, Hulbert, & Berghoff LLP, of Chicago, Illinois, argued for defendant-appellee. With him on the brief were Curt J. Whitenack, James C. Gumina, Jeremy E. Noe, and Paul S. Tully. Of counsel on the brief was Joseph Kirk, Jr., Aventis Pharmaceuticals Inc., of Bridgewater, New Jersey.

Appealed from: United States District Court for the District of Delaware

Judge Joseph J. Farnan, Jr.

United States Court of Appeals for the Federal Circuit

05-1313

IMPAX LABORATORIES, INC.,

Plaintiff-Appellant,

v.

AVENTIS PHARMACEUTICALS INC.,

Defendant-Appellee.

DECIDED: November 20, 2006

Before RADER, SCHALL, and PROST, Circuit Judges.

Opinion for the court filed by Circuit Judge SCHALL. Concurring-in-part opinion filed by Circuit Judge RADER.

SCHALL, Circuit Judge.

Impax Laboratories, Inc. ("Impax") sued Aventis Pharmaceuticals Inc. ("Aventis") in the United States District Court for the District of Delaware for a declaratory judgment that Impax did not infringe, induce infringement of, or contribute to the infringement of, U.S. Patent No. 5,527,814 ("the '814 patent") under 35 U.S.C. § 271(e)(2) by filing an Abbreviated New Drug Application ("ANDA"). In its suit, Impax alleged, inter alia, that the '814 patent was invalid and unenforceable. Impax filed its ANDA under the provisions of the Patent Laws and Drug Price Competition and Patent Term Restoration

Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984), codified at 21 U.S.C. §§ 355, 360(c) (2000), 35 U.S.C. §§ 156, 271, and 282 (2000) (commonly referred to as the "Hatch-Waxman Act"). In its ANDA, Impax sought the approval of the United States Food and Drug Administration ("FDA") to engage in the commercial manufacture and/or sale of riluzole tablets for the treatment of patients with amyotrophic lateral sclerosis ("ALS").

Impax now appeals from the decision of the district court, following a bench trial, that it failed to prove (1) that the '814 patent is unenforceable due to inequitable conduct and (2) that claims 1-5 of the '814 patent are invalid as anticipated. See Impax Labs., Inc. v. Aventis Pharms., Inc., 333 F. Supp. 2d 265 (D. Del. 2004) ("Validity and Enforceability Order"). We see no error in the decision of the district court on the inequitable conduct issue. However, as far as the anticipation issue is concerned, we conclude that the court erred in its determination that one of the alleged two items of invalidating prior art did not enable a method of using riluzole to treat ALS and, therefore, could not serve as an anticipatory reference under 35 U.S.C. § 102(b). Accordingly, we affirm-in-part, vacate-in-part, and remand.

BACKGROUND

I.

A.

Impax is a Delaware corporation with its principal place of business in Hayward, California. Aventis is a Delaware corporation with its principal place of business in Bridgewater, New Jersey. Aventis was formed in 1999 as part of a merger between

Rhone-Poulenc, S.A., ("RP") and Hoechst, AG.[1] Aventis owns the '814 patent, which involves the use of riluzole to treat ALS. Aventis sells riluzole under the trade name Rilutek.

B.

ALS, commonly referred to as Lou Gehrig's disease, is a disease of the central nervous system. It involves the progressive degeneration of the nerves that carry impulses to muscles. ALS is characterized by the death of the nerves that control motor function (also called motor neurons). This occurs after the motor neuron cell bodies shrivel and harden, a process called sclerosis. The clinical symptoms of ALS may first appear in the skeletal muscles, referred to as "limb onset" ALS, or in the bulbar muscles of the throat, tongue, and respiratory system, referred to as "bulbar onset" ALS.

Riluzole is the chemical compound 6-trifluoromethoxy-2-benzothiazolamine. In 1993 and 1994, Aventis conducted comparative testing of riluzole and seven other compounds, Pharm 1001 through 1007, on dissociated rat spinal cord cells. The purpose of the testing was to determine whether the compounds would be effective in treating ALS. Dr. Louvel sent riluzole and the other seven compounds to a research facility in Uruguay for analysis. The effects of riluzole and the other compounds on the rat spinal cords were analyzed based on the following criteria: (1) number of neurons in the cells (used to screen for extraneous effects of the compound); (2) number of neurites per neuron[2] (thought to indicate effectiveness in treating ALS); and (3)

[1] At the time the '814 patent was prosecuted, Dr. Eric Louvel, the inventor, worked for Rhone Poulenc Rorer, S.A. ("RPR"). RP was the parent company of RPR. For simplicity, during the discussion of the prosecution history of the '814 patent, we refer to Aventis as the prosecuting party.

[2] A neurite is a projection from a neuron.

neuronal diameter (thought to indicate neuronal health and to be pertinent to treating ALS).

The 1993 tests compared riluzole to compounds identified as Pharm 1001 through Pharm 1004 ("the 1993 comparative test data"). The 1993 study concluded:

> None of PHARM compounds showed the same pattern of effects than [sic] Riluzole. PHARM 1001 and 1003 were toxic for motoneurons, while PHARM 1003 also decreased the number of neurites per neuron. PHARM 1002 was observed to stimulate the growth of the cultures and to increase the size of neurons. PHARM 1004 showed no relevant effects.

The 1994 set of tests compared riluzole to compounds identified as Pharm 1005 through Pharm 1007 ("the 1994 comparative test data"). The 1994 study concluded: "None of PHARM compounds tested showed the same pattern of effects than [sic] Riluzole: PHARM 1005 and PHARM 1006 induced an important decrease in neuronal cell number (including motoneurons) and prevented the development and differentiation of neurons. The effects of PHARM 1007 were not significantly different from control conditions."

C.

In due course, the '814 patent issued from U.S. Patent Application Serial No. 08/327,343 ("the '343 application"), filed October 21, 1994, which claimed priority to U.S. Patent Application Serial No. 07/945,789 ("the '789 application"), filed September 16, 1992. The '343 application and the '789 application both were directed to treating ALS with riluzole.

On November 19, 1993, the examiner issued a final rejection of the claims of the '789 application based on obviousness in light of certain prior art. The examiner asserted that the prior art disclosed that ALS "is a motor neuron disease or disorder

which may be treatable in humans with antiglutamate agents" and that "riluzole is known to be a glutamate antagonist useful for the treatment of motor neurons in mammals." (It had been theorized that excitatory amino acids, such as glutamates, may be involved in ALS.) On that basis, the examiner concluded that "[o]ne of ordinary skill in the art would have been motivated . . . to employ riluzole in the treatment of any form of the motor neuron disease, ALS, since riluzole was known in the art as an antiglutamate agent, and antiglutamate agents were known in the art for the treatment of ALS."

Responding on May 24, 1994, Aventis relied on the 1994 comparative test data relating to Pharm 1006 (6-pentafluoroethoxy-2- benzothiazolamine) and Pharm 1007 (6-(1,1,2,2-tetrafluoroethoxy)-2-benzothiazolamine). Both are compounds disclosed in U.S. Patent No. 5,236,940 ("the '940 patent"), which the examiner referred to as "pertinent to the applicant's disclosure." Aventis stated that Pharm 1006 and Pharm 1007 constituted "evidence of the non-obviousness of the instant claims" over the prior art relied upon by the examiner. Aventis explained that riluzole, Pharm 1006, and Pharm 1007 were compared in two tests on dissociated spinal cord cell cultures as to the number of neurites per neuron and neuron diameter. Aventis stated that positive results were shown for riluzole:

> The most striking effects are:
> 1) increased number of neurites per neuron; and
> 2) increased number of large neurons.
> These results are urged to be unexpected and not predictable from the prior art. The Examiner should note that the compound Pharm 1006 presents an opposite action and compound Pharm 1007 is inactive. The effects shown for Riluzole permit the use of this compound for the treatment of motor neuron diseases, in particular, ALS.

A May 24, 1994 declaration from Dr. Louvel accompanied the response and discussed the testing methodology and 1994 comparative test data obtained for riluzole and

Pharm 1006 and Pharm 1007. The same declaration was submitted on February 6, 1995, during prosecution of the continuing '343 application, an application that claimed priority to the later abandoned '789 application.

On February 21, 1995, the examiner rejected the claims of the '343 application as obvious based on several prior art references, including a prior art reference authored by Dr. Theodore Munsat. The examiner challenged the testing procedure resulting in the 1994 comparative test and described in the February 6, 1995 Louvel declaration as providing unexpected results: "Applicant has not demonstrated that the testing procedure discussed in the declaration would be accepted by one of ordinary skill in the art as showing the activity of compounds in the claimed methods of treatment." The examiner then explained that the February 6, 1995 declaration had been considered but was "deemed not persuasive to overcome the rejection under 35 U.S.C. 103."

In April 5, 1995, June 6, 1995, and September 20, 1995 interviews with the examiner and in a June 19, 1995 response, Aventis asserted that the 1994 comparative test data on Pharm 1006 and Pharm 1007 and other evidence indicated that the invention had unexpected results. A June 22, 1995 declaration from Dr. Louvel asserted that the testing procedure that was used to compare the Pharm 1006 and Pharm 1007 compounds to riluzole was well-established.

Thereafter, on September 27, 1995, Aventis obtained new patent prosecution counsel and stated to the examiner that the June 19, 1995 response was "fully responsive" to the February 21, 1995 Office Action. Aventis then withdrew "reliance on all previous arguments and declarations." Aventis also submitted a declaration from Dr.

Munsat (as noted, the author of one of the prior art references cited by the examiner) that stated that by the priority date of the ’814 patent one of ordinary skill in the art would have had no reasonable expectation of success in using riluzole to treat ALS because of the failure of other glutamate antagonists to effectively treat ALS.

On March 1, 1996, the examiner issued a Notice of Allowability specifically referencing amendments and remarks from the June 19, 1995 response, the Munsat declaration, and the September 27, 1995 response. The applicants responded that they viewed the application as “allowed solely because of the September 27, 1995, Amendment and Declaration of Dr. Munsat.” The ’814 patent issued on June 18, 1996, and names Dr. Louvel as the sole inventor.

D.

Claims 1-5 are the only claims of the ’814 patent that are at issue in this case. Independent claim 1 claims “[a] method for treating a mammal with [ALS], comprising the step of administering to said mammal in recognized need of said treatment an effective amount of [riluzole] or a pharmaceutically acceptable salt thereof.” ’814 patent, claim 1. Claims 2 through 4 each depend on claim 1. Id., claims 2-4. Claim 2 adds the limitation that the form of ALS being treated involves “early bulbar involvement.” Id., claim 2. Claim 3 adds the limitation that the form of ALS being treated “is the bulbar form.” Id., claim 3. Claim 4 adds the limitation that the effective amount of compound being administered comprises 25 to 200 mg of riluzole. Id., claim 4. Claim 5 depends from claim 4 and claims the administration of riluzole in an amount of 50 mg. Id., claim 5.

II.

A.

Pursuant to the Hatch-Waxman Act, section 505 of the Federal Food, Drug, and Cosmetic Act, codified at 21 U.S.C. § 355, was amended to authorize the filing of ANDAs. 21 U.S.C. § 355; see also Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1358 (Fed. Cir. 2003). Under 35 U.S.C. § 271(e)(2), it is an act of infringement to submit an ANDA under 21 U.S.C. § 355(j) for a drug claimed in a patent before the patent's expiration:

> It shall be an act of infringement to submit—(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act . . . for a drug claimed in a patent or the use of which is claimed in a patent, . . . if the purpose of such submission is to obtain approval under such Act [i.e., Title 21 of the United States Code] to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

35 U.S.C. § 271(e)(2) (2000).

On March 16, 2001, Impax filed an ANDA with the FDA under 21 U.S.C. § 355(j), seeking approval to market and sell generic riluzole tablets for the treatment of ALS. The FDA approved Impax's ANDA on January 29, 2003. At the time that Impax filed its ANDA, there was no patent listed with respect to riluzole in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), which lists patents that claim an approved or pending use of a new drug.[3] However, Impax became aware of the '814 patent while preparing its ANDA.

On June 25, 2002, Impax filed a declaratory judgment action in the District of Delaware. In its suit, Impax sought a declaration that it had not infringed the '814 patent

[3] See 21 C.F.R. § 314.53; Warner-Lambert, 316 F.3d at 1361 n.6.

under 35 U.S.C. § 271(e)(2) by filing its ANDA, and that it would not contribute to or induce infringement of any valid claim of the '814 patent by engaging in the manufacture and sale of its riluzole product for the treatment of ALS. Impax asserted that the claims of the '814 patent were invalid over the prior art and invalid by reason of incorrect inventorship. Impax later amended its complaint to add allegations of inequitable conduct. On December 12, 2002, the district court entered a preliminary injunction against Impax, barring it from marketing its riluzole product. Impax Labs., Inc. v. Aventis Pharms., Inc., 235 F. Supp. 2d 390 (D. Del. 2002). On April 29, 2003, the parties entered into a stipulation whereby Impax conceded that its ANDA product infringed claims 1, 4, and 5 of the '814 patent.

B.

From October 28 to 30, 2003, the district court conducted a bench trial on the issues of (1) whether claims 1-5 of the '814 patent were unenforceable due to inequitable conduct, (2) whether claims 1-5 of the '814 patent were invalid as anticipated, as obvious, or by reason of incorrect inventorship, and (3) whether Impax infringed claims 2-3 of the '814 patent or induced such infringement. See Validity and Enforceability Order, 333 F. Supp. 2d at 268. On August 30, 2004, the district court issued a Memorandum Opinion and Order, concluding that Impax had not proven that the '814 patent was unenforceable due to inequitable conduct or demonstrated that claims 1-5 were invalid as anticipated by the prior art cited by Impax. Id. at 265. The court also rejected Impax's assertion that claims 1-5 of the '814 patent were invalid by reason of obviousness or for incorrect inventorship. Id. at 276. With respect to obviousness, the court held that Impax had not proven, by clear and convincing

evidence, that the prior art upon which Impax relied rendered the claims obvious. Id. at 274-76. With respect to inventorship, the court found that the allegation was "unduly speculative and not supported by evidence sufficient to support a finding of invalidity." Id. at 276. Finally, in a footnote, the court declined to address whether Impax's proposed marketing of riluzole would induce infringement of claims 2 and 3 of the '814 patent because "Impax may not engage in the manufacture or sale of riluzole regardless of whether its proposed actions would induce infringement of claims 2 and 3 of the '814 patent."[4] Id. at 284 n.5.

On March 16, 2005, the district court entered final judgment against Impax, to the effect that claims 1-5 of the '814 patent were neither unenforceable nor invalid, that Impax's proposed manufacture or sale of riluzole would induce infringement of claims 1, 4, and 5 of the '814 patent, and that lmpax's proposed marketing of riluzole to treat ALS would induce infringement of claims 2 and 3 of the '814 patent.

On March 21, 2005, Impax filed a timely notice of appeal. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

Impax appeals the district court's determination that it failed to prove (1) that the '814 patent is unenforceable due to inequitable conduct and (2) that the '814 patent is invalid as anticipated. We address these contentions in turn.

[4] This was because Impax had conceded infringement of claims 1, 4, and 5.

I.

A.

To prove that a patent is unenforceable due to inequitable conduct, the alleged infringer must provide clear and convincing evidence of (1) affirmative misrepresentations of a material fact, failure to disclose material information, or submission of false material information and (2) an intent to deceive. Alza Corp. v. Mylan Labs., Inc., 391 F.3d 1365, 1373 (Fed. Cir. 2004).

The materiality aspect of inequitable conduct was recently discussed in Digital Control Inc. v. Charles Machine Works, 437 F.3d 1309 (Fed. Cir. 2006). In that case, we considered the standard for materiality set forth in the present version of U.S. Patent and Trademark Office ("PTO") Rule 56, see 37 C.F.R. § 1.56(b) (2004), as well as the previous version of the rule, that was in effect through 1992. Digital Control, 437 F.3d at 1314. We explained that "if a misstatement or omission is material under the new Rule 56 standard, it is material. Similarly, if a misstatement or omission is material under the 'reasonable examiner' standard or under the older three tests,[5] it is also material." Id. at 1316. The present Rule 56 standard is as follows:

> Information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and
>
> (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

[5] The "older three tests" include (1) the objective "but for" standard, "where the misrepresentation was so material that the patent should not have issued," (2) the subjective "but for" test, "where the misrepresentation actually caused the examiner to approve the patent application when he would not otherwise have done so," and (3) the "but it may have" standard, "where the misrepresentation may have influenced the patent examiner in the course of prosecution." Digital Control, 437 F.3d at 1315.

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office, or

(ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

37 C.F.R. § 1.56(b) (2006). Under the prior "reasonable examiner" standard, an omission or misstatement was material if "a reasonable examiner would have considered such prior art important in deciding whether to allow the parent application." Digital Control, 437 F.3d at 1314 (citations omitted).

As seen, inequitable conduct also requires an intent to deceive. To satisfy the intent to deceive element of inequitable conduct, "the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." Kingsdown Med. Consultants, Ltd. v. Hollister, Inc., 863 F.2d 867, 876 (Fed. Cir. 1988) (en banc in relevant part). "Intent need not, and rarely can, be proven by direct evidence." Merck & Co. v. Danbury Pharmacal, Inc., 873 F.2d 1418, 1422 (Fed. Cir. 1989). Rather, intent to deceive is generally inferred from the facts and circumstances surrounding the applicant's overall conduct. Id.

If the court finds materiality and intent, it "must balance the equities to determine whether the patentee has committed inequitable conduct that warrants holding the

patent unenforceable." Monsanto Co. v. Bayer BioScience N.V., 363 F.3d 1235, 1239 (Fed. Cir. 2004). The more material the omission or misrepresentation, the less intent that must be shown to elicit a finding of inequitable conduct. Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc., 326 F.3d 1226, 1234 (Fed. Cir. 2003). If inequitable conduct occurred with respect to one or more claims of an application, the entire patent is unenforceable. Kingsdown Med. Consultants, 863 F.2d at 877.

We review a district court's ultimate decision on a claim of inequitable conduct for an abuse of discretion and its threshold findings on materiality and intent for clear error. Alza, 391 F.3d at 1369-70. An abuse of discretion occurs when (1) the court's decision is clearly unreasonable, arbitrary, or fanciful, (2) the court's decision is based on an erroneous construction of the law, (3) the court's factual findings are clearly erroneous, or (4) the record contains no evidence upon which the court rationally could have based its decision. See, e.g., Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1460 (Fed. Cir. 1998) (en banc). Under the clear error standard, the court's findings will not be overturned in the absence of a "definite and firm conviction" that a mistake has been made. Hoffmann-La Roche, Inc. v. Promega Corp., 323 F.3d 1354, 1359 (Fed. Cir. 2003) (quoting Molins PLC v. Textron, Inc., 48 F.3d 1172, 1180 (Fed. Cir. 1995)).

B.

Before the district court, Impax's main contention in support of its claim of inequitable conduct—and the contention that is relevant on appeal—was that, during prosecution of the '789 application and the continuing '343 application, Aventis withheld from the examiner the 1993 comparative test data relating to the testing of Pharm 1001 through Pharm 1004, and the 1994 comparative test data relating to the testing of

Pharm 1005. According to Impax, the withheld data was material because it was inconsistent with an argument advanced by Aventis in support of patentability during prosecution. Aventis responded that the information that was not provided to the examiner was immaterial, superfluous, or less pertinent than the disclosed information. The district court ruled that under either the materiality standard of the current version of Rule 56 or equitable principles (i.e., the rules based on the pre-1992 version of Rule 56) Impax had not proven inequitable conduct. Validity and Enforceability Order, 333 F. Supp. 2d at 277. Considering the alleged withholding of the 1993 comparative test data, the court concluded that "Aventis's partial disclosure of the comparative test results was not inappropriate." Id. at 279-81. The court found that the withheld 1993 and 1994 comparative test data was not material because (1) the results for Pharm 1002,[6] Pharm 1003, and Pharm 1005 were not inconsistent with the representation to the examiner that riluzole was better than Pharm 1006 and Pharm 1007, which were the subject of the 1994 comparative test data; (2) "the withheld comparative testing did not produce results that indicated effectiveness in treating ALS," because while Pharm 1002 produced increases in neuron diameter and neurites per neuron, it only produced "significant" increases in neuron diameter; (3) the "patent examiner explicitly excluded the submitted testing [Pharm 1006 and Pharm 1007] from her decision" because "'the applicant has not demonstrated that the testing procedures discussed in the declaration would be accepted by one of ordinary skill in the art as showing the activity of compounds in the claimed method of treatment'"; and (4) "the comparative test results were not as valuable as the results of human clinical trials which were submitted to the

[6] Pharm 1002 is disclosed in U.S. Patent No. 5,026,717, which formed the basis for an initial obviousness rejection by the examiner.

PTO." Id. at 280-81. The district court suggested that even if it did find a "minimal level of materiality" there was an absence of intent to deceive. Id. Thus, the district court concluded that there was no inequitable conduct in the prosecution of the '814 patent. Id.

C.

On appeal, Impax repeats its claim that Aventis committed inequitable conduct by withholding the 1993 comparative test data and the 1994 comparative test data relating to Pharm 1005. According to Impax, that data was inconsistent with a position that Aventis took in its May 24, 1994 response. In its response, which relied on Dr. Louvel's May 24, 1994 declaration pursuant to 37 C.F.R. § 1.132, Aventis argued that the invention was patentable because it showed unexpected results over Pharm 1006 and Pharm 1007.

Impax argues that Dr. Louvel's declaration withheld data for certain prior art compounds (Pharm 1002 and Pharm 1003, included in the 1993 comparative test data, and Pharm 1005, included in the 1994 comparative test data) that had positive results for key criteria. Specifically, Impax argues that the 1993 comparative test data demonstrates that Pharm 1002 and Pharm 1003, along with riluzole, had the highest increase of neurites per neuron and that Pharm 1002 had the greatest absolute values in increased diameter of neuron cells. Impax contends that Pharm 1002 presented positive results in two of the same parameters in which riluzole tested positive, while Pharm 1006 and Pharm 1007 did not, so Pharm 1002 is "superior" to Pharm 1006 and Pharm 1007. Thus, Impax concludes, Dr. Louvel failed to disclose positive test data for Pharm 1002, which data undermined the argument Aventis was making in prosecution

that its riluzole compound showed unexpected results in the treatment of ALS (as compared to Pharm 1006 and Pharm 1007). As far as the 1994 comparative test data is concerned, Impax argues that the data demonstrates that Pharm 1005 and riluzole had the largest increase in neuron cell diameter. Impax rejects the district court's three reasons for finding the information immaterial. First, Impax asserts that the withheld information is inconsistent because Dr. Louvel asserted in prosecution that riluzole had unexpected results. Therefore, it was inconsistent to withhold test results that exhibited better results for other compounds. Second, Impax argues that it is irrelevant that the withheld data does not indicate effectiveness in treating ALS because it was "clearly better than the data that Dr. Louvel supplied" and thus material.

Aventis responds that Impax misrepresents the comparative test data because, while Pharm 1002 and Pharm 1005 were positive in neuron diameter, they were not significantly different from the control in neurites per neuron, while Pharm 1001 and 1003 were toxic for motoneurons, and only riluzole was positive in all parameters tested. Further, Aventis asserts that the reported data was consistent with Aventis's statements to the examiner because the 1994 comparative test data on Pharm 1006 and Pharm 1007 served to distinguish the '814 patent from the '940 patent, while the unreported 1993 comparative test data was related to compounds that were not in the '940 patent.

D.

We see no error in the ruling of the district court that the 1993 comparative test data and the 1994 comparative test data on Pharm 1005 were not material under either Rule 56 standard. There is no evidence that the withheld comparative test data

establishes by itself or in combination with other information a prima facie case of unpatentability of a claim. In our view, the district court correctly recognized that the comparative test data did not produce results that indicated that any of Pharm 1002, 1003, or 1005 was effective in treating ALS. As the district court recognized,

> [a]lthough some of the Pharm compounds produced significant positive results in one of the two relevant parameters—an increase in neurites per neuron or an increase in neuron diameter—none of the Pharm compounds from the withheld tests produced results significant in both parameters. For example, Pharm 1002 produced increases in neuron diameter and neurites per neuron, but only produced significant increases in neuron diameter.

Validity and Enforceability Order, 333 F. Supp. 2d at 280.

Further, there is no evidence that the withheld comparative test data refutes or is inconsistent with a position Aventis took during prosecution. Aventis submitted correct information, and Impax does not argue that the submitted comparative testing data was false. We see no error in the district court's determination that the results for Pharm 1002, Pharm 1003, and Pharm 1005 were not inconsistent with the representation to the examiner that riluzole was better than Pharm 1006 and Pharm 1007. The comparative test data in this case was submitted to demonstrate unexpected results based on compositions in the '940 patent—namely Pharm 1006 and Pharm 1007. Aventis never suggested that this was the only testing data or that another compound, such as Pharm 1002, was not tested.

Finally, there is no evidence that a reasonable examiner "would have considered such prior art important in deciding whether to allow the parent application." Digital Control, 437 F.3d at 1314. As discussed above, the 1993 comparative test data and the

1994 comparative test data on Pharm 1005 did not produce results that indicated effectiveness in treating ALS.

Reviewing the district court's finding on materiality for clear error, we are not left with a definite and firm conviction that a mistake has been committed.

Nor did the district court clearly err in its intent findings. The district court concluded after a bench trial that there was an "absence" of intent. Validity and Enforceability Order, 333 F. Supp. 2d at 281. As far as intent is concerned, Impax asserts that the 1993 and 1994 comparative test data were withheld with an intent to deceive. First, Impax argues that misrepresentations and omissions in a declaration are presumptively intentional. Next, Impax asserts that the circumstances surrounding prosecution demonstrate an intent to deceive because of the submission of the declaration and the materiality of the withheld information. Finally, Impax argues that Dr. Louvel, who was involved in the preparation and prosecution of the '814 patent, was aware of the 1993 comparative test data and the comparative test data on Pharm 1005, but he chose to disclose only the 1994 comparative test data on Pharm 1006 and Pharm 1007.

Aventis responds that there is no clear and convincing evidence of intent to deceive. It argues that Impax's citations to internal Aventis documents suggesting that Aventis did not have faith in the strength of the application do not demonstrate an intent to deceive. It distinguishes Impax's reliance on cases involving false statements in declarations, arguing that there was no false information in the Louvel declaration.

We cannot say that the district court's finding that there was no intent amounts to clear error. Dr. Louvel was involved in both the 1993 and 1994 testing and the

prosecution of the ’814 patent. He did disclose the data relevant to distinguishing the ’940 patent—the 1994 comparative test data on Pharm 1006 and Pharm 1007—but he did not disclose the comparative test data that would be irrelevant to distinguishing the ’940 patent. We agree with the district court that these facts, standing alone, are not enough to establish an intent to deceive. As the district court recognized, there was no evidence that Impax intended to deceive the PTO when it did not disclose the 1993 comparative test data or the comparative test data on Pharm 1005.

We thus affirm the district court’s ruling that the ’814 patent is not unenforceable by reason of inequitable conduct.

II.

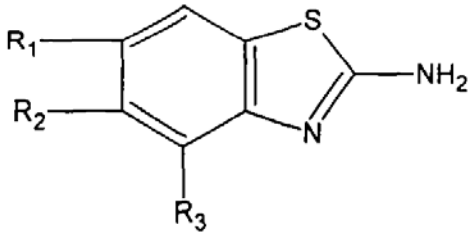
A.

An issued patent is presumed to be valid, and the burden of establishing invalidity as to any claim of a patent rests upon the party asserting such invalidity. 35 U.S.C. § 282. Clear and convincing evidence is required to invalidate a patent. Typeright Keyboard Corp. v. Microsoft Corp., 374 F.3d 1151, 1157 (Fed. Cir. 2004). When the prior art was before the examiner during prosecution of the application, there is a particularly heavy burden in establishing invalidity. See Hewlett-Packard Co. v. Bausch & Lomb Inc., 909 F.2d 1464, 1467 (Fed. Cir. 1990).

In the district court Impax claimed that claims 1-5 of the ’814 patent were anticipated by the ’940 patent[7] and French Application No. 2,640,624 (“the ’624 application”), from which the ’940 patent claims priority. The pertinent facts are as follows:

[7] As noted above, during prosecution of the ’789 application, the examiner cited the ’940 patent as pertinent prior art.

On December 13, 1989, the application that matured into the '940 patent was filed. The '940 patent, which is owned by Aventis, is directed to a class of compounds disclosed in formula I below:



'940 patent, col.1, ll.10-66. The '940 patent explains that formula I includes many different compounds, but it exempts 6-trifluoromethoxy-2-benzothiazolamine. Id., col.1. ll.10-37. That is, 6-trifluoromethoxy-2-benzothiazolamine, also known as riluzole, is a compound that could fall within the literal scope of formula I but is explicitly exempted from formula I by the specification of the '940 patent. The '940 patent explains that 6-trifluoromethoxy-2-benzothiazolamine is not new, and thus does not form part of the invention. Id., col.1. ll.41-47.

The '940 patent goes on to state that the compounds of formula I are useful in treating medical conditions associated with the effects of glutamate such as ALS:

> The compounds of formula (I) and their salts possess advantageous pharmacological properties. These compounds are useful in the treatment of medical conditions associated with the effects of glutamate in which it is desirable to inhibit such effects at least partially. They are active with respect to glutamate-induced convulsions, and are hence useful in the treatment and prevention of convulsive phenomena, schizophrenic disorders, and in particular the deficiency forms of schizophrenia, sleep disorders, phenomena linked to cerebral ischaemia and also neurological conditions in which glutamate may be implicated, such as Alzheimer's disease, Huntington's chorea, [ALS] and olivopontocerebellar atrophy.

'940 patent, col.2. l.63 to col.3, l.8 (emphases added).

The ’940 patent claims priority from the ’624 application, which has a disclosure similar to that of the ’940 patent. However, the ’624 application does not exempt 6-trifluoromethoxy-2-benzothiazolamine from the family of formula I compounds as a claimed compound.

B.

Before the district court, Impax argued that every limitation of claims 1-5 of the ’814 patent was disclosed by the ’940 patent. Impax asserted that the ’940 patent disclosed a class of compounds generally encompassed by formula I, including riluzole, and that the ’940 patent taught that riluzole is useful in treating ALS and also taught effective administration. Because the ’940 patent claims priority from the ’624 application and contains similar disclosures, Impax asserted virtually identical arguments with respect to the ’624 application. Aventis responded that the ’940 patent excluded riluzole from the compounds in formula I. Aventis asserted in addition that even if the ’940 patent included riluzole, it did not anticipate the ’814 patent because it failed to disclose the invention in the ’814 patent and was not enabling because it did not provide specific instruction for using riluzole and actually taught away from riluzole. It asserted similar arguments with respect to the ’624 application.

The district court agreed with Impax that formula I of the ’940 patent included riluzole, but concluded that the ’814 patent was not anticipated because “formula I entails such a large number of compounds . . . [that] one of ordinary skill in the art would not have recognized that riluzole was effective in treating ALS without additional detail or guidance that is not found in the disclosure of the ’940 patent.” Validity and

Enforceability Order, 333 F. Supp. 2d at 272 (emphasis added).[8] The court reasoned that riluzole was not listed as one of the "especially advantageous" compounds, that riluzole was not meaningfully discussed in the '940 patent, and that the language of the '940 patent demonstrated that there was "substantial uncertainty regarding the effectiveness of treating ALS with glutamate inhibiting compounds." Id. (emphasis added). The district court concluded that the language in the '940 patent which indicated that formula I compounds will treat "neurological conditions in which glutamate may be implicated" amounted to speculation that those compounds would be useful in treating ALS. Id. The court stated: "[O]ne of ordinary skill in the art would not have recognized riluzole's effectiveness in treating ALS, and therefore, the Court finds that the '940 patent does not anticipate the '814 patent." Id. (emphasis added). Thus, the court apparently determined that even though formula I of the '940 patent includes riluzole, the formula did not anticipate the '814 patent because it did not disclose riluzole as being effective in treating ALS. Therefore, the court reasoned, formula I was not enabling.

The district court explained that the '624 application, from which the '940 patent claims priority, contained a disclosure similar to the '940 patent and that the parties asserted virtually identical arguments with respect to the two disclosures. Id. Thus, it concluded that there were no material differences between the two references that persuaded the court to reach a conclusion different from the one it had reached with respect to the '940 patent. Id. Having decided that the '940 patent and the '624

[8] The district court's statements about riluzole in the prior art being effective in treating ALS are unrelated to the words "effective amount" in the claims of the '814 patent.

application were not enabling, the district court did not address whether they anticipated claims 1-5 of the ’814 patent.

C.

On appeal, Impax argues that the ’940 patent enables treating ALS with riluzole because it provides sufficient guidance to allow one of ordinary skill in the art to determine riluzole’s actual effectiveness against ALS without undue experimentation, as the ’940 patent indicates that the compounds of formula I are active against ALS and specifies the dosage ranges to be given. Impax also argues that the ’624 application anticipates the ’814 patent, but acknowledges that the ’624 application does not exclude riluzole from the compounds included in formula I.

Aventis responds that the ’940 patent—which was considered during prosecution but was not viewed by the examiner as supporting a rejection of the pending claims—does not enable a method of using riluzole to treat ALS, as the ’940 patent discloses hundreds of possible compounds, does not meaningfully discuss riluzole or identify it as a medication, indicates that the compounds of formula I may be useful in treating “a laundry list of diseases,” and offers only “speculation” that the formula I compounds might treat ALS. Aventis further argues that there was no evidence that a person of skill in the art would find the ’940 patent “to indicate efficacy against ALS,” that the district court correctly found that there was uncertainty as to whether riluzole would work to treat ALS, and that the gaps in the ’940 patent cannot be filled by extrinsic knowledge because no such extrinsic knowledge existed. Aventis contends that Impax’s expert, Dr. Jeffery Rothstein, was unable to identify any specific teaching in the ’940 patent that would have led one to riluzole, while its expert, Dr. Benjamin Brooks, testified that one

skilled in the art would not have had a reasonable expectation of success in treating ALS based on the disclosure of the '940 patent. Aventis posits that the decision regarding the '940 patent would be applicable to the '624 application.

D.

An invention is anticipated if it "was . . . described in a printed publication in this . . . country . . . more than one year prior to the date of application for patent in the United States." 35 U.S.C. § 102(b) (2000). A patent claim is invalid as anticipated if every limitation in a claim is found in a single prior art reference, either explicitly or inherently. See MEHL/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1365 (Fed. Cir. 1999). "Anticipation is a factual matter, which we review under the clearly erroneous standard." Glaxo v. Novopharm, 52 F.3d 1043, 1047 (Fed. Cir. 1995).

In order to be anticipating, a prior art reference must be enabling so that the claimed subject matter may be made or used by one skilled in the art. Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1354 (Fed. Cir. 2003); Helifix, Ltd. v. Blok-Lok, Ltd., 208 F.3d 1339, 1346 (Fed. Cir. 2000); Akzo N.V. v. U.S. Int'l Trade Comm'n, 808 F.2d 1471, 1479 (Fed. Cir. 1986). Prior art is not enabling so as to be anticipating if it does not enable a person of ordinary skill in the art to carry out the invention. See Elan Pharms., Inc. v. Mayo Found., 346 F.3d 1051, 1057 (Fed. Cir. 2003) (remanding the case to the district court for a determination of whether the prior art reference enabled persons of ordinary skill to make the invention without undue experimentation); In re Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985) ("[P]rior art . . . must sufficiently describe the claimed invention to have placed the public in possession of it. Such possession is effected if one of ordinary skill in the art could have combined

the publication's description of the invention with his own knowledge to make the claimed invention.") (citation omitted).

The enablement requirement for prior art to anticipate under section 102 does not require utility, unlike the enablement requirement for patents under section 112.[9] Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1325-26 (Fed. Cir. 2005) ("[A] prior art reference need not demonstrate utility in order to serve as an anticipating reference under section 102." (citing In re Schoenwald, 964 F.2d 1122, 1124 (Fed. Cir. 1992); In re Donohue, 632 F.2d 123, 126 n.6 (C.C.P.A. 1980)); see also In re Samour, 571 F.2d 559, 563-64 (C.C.P.A. 1978); In re Hafner, 410 F.2d 1403, 1405 (C.C.P.A. 1969). In Rasmusson, we held that the Board of Patent Appeals and Interferences ("Board") erred in determining that a prior art reference was not enabling and thus not anticipatory. 413 F.3d at 1325-26. The patent application in Rasmusson claimed a method of treating prostate cancer by using a chemical called finasteride. Id. at 1320. The prior art reference disclosed a method of treating prostate cancer by using finasteride, but the Board found that the prior art reference was not enabling because it failed to demonstrate that finasteride was "effective" in treating prostate cancer. Id. at 1325-26. We reversed the Board's determination that the prior art was not enabling and remanded the case for consideration of anticipation, holding that proof of efficacy is not required for a prior art reference to be enabling under section 102. Id.; see also Novo

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[9] Section 112, paragraph 1 states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

35 U.S.C. § 112, ¶ 1 (2000).

Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp., 424 F.3d 1347, 1355 (Fed. Cir. 2005) ("The standard for enablement of a prior art reference for purposes of anticipation under section 102 differs from the enablement standard under 35 U.S.C. § 112. . . . While section 112 'provides that the specification must enable one skilled in the art to "use" the invention,' . . . 'section 102 makes no such requirement as to an anticipatory disclosure,' . . . . Significantly, we have stated that 'anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabled to one of skill in the art.'" (citations omitted)); Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1378 (Fed. Cir. 2001) (holding that prior art that suggested a drug was ineffective nevertheless anticipated a patent on that drug); Celeritas Techs. v. Rockwell Int'l Corp., 150 F.3d 1354, 1361 (Fed. Cir. 1998) ("A reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. Thus, the question whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis.").

"Whether a prior art reference is enabling is a question of law based upon underlying factual findings." Minn. Mining & Mfg. Co. v. Chemque, Inc., 303 F.3d 1294, 1301 (Fed. Cir. 2002). In Amgen, we stated that, when, as here, an accused infringer asserts that either claimed or unclaimed material in a prior art patent anticipates patent claims asserted against it, the infringer is entitled to a presumption that the allegedly anticipating material is enabled. 314 F.3d at 1355 ("[A] court cannot ignore an asserted prior art patent in evaluating a defense of invalidity for anticipation, just because the accused infringer has not proven it enabled."). However, "[i]f a patentee presents evidence of nonenablement that a court finds persuasive, the trial court must then

exclude the particular prior art patent in any anticipation inquiry, for then the presumption has been overcome." Id. In this case, the issue is whether the prior art enables the treatment of a specific disease with a specific compound.

E.

We turn first to the question of whether the '940 patent is an enabling prior art reference. Riluzole is a compound of formula I in the '940 patent. At the same time, the '940 patent recognizes that the compounds of formula I of the '940 patent possess "advantageous pharmacological properties" and "are active with respect to glutamate induced convulsions, and are hence useful in the treatment and prevention of . . . neurological conditions in which glutamate may be implicated, such as . . . [ALS] . . . ." '940 patent col.2, l.63 to col.3, l.8. The '940 patent explains that the dosages of the compounds in formula I "depend on the effect sought, the treatment, period and the administration route used," but that they are "generally between 30 and 300 mg per day in oral administration for an adult, with unit doses ranging from 10 to 100 mg of active substance." However, "the doctor will determine appropriate dosage in accordance with the age and weight and all other factors characteristic of the subject to be treated." While the '940 patent includes riluzole as a formula I compound, suggests that formula I compounds may be used to treat ALS, and provides some dosage information, the district court found that the '940 patent did not anticipate the '814 patent because the disclosure of the '940 patent was not enabling at least in part because there was no evidence that it would be "effective." Validity and Enforceability Order, 333 F. Supp. 2d at 272. However, as we recognized in Rasmusson, proof of efficacy is not required for a prior art reference to be enabling for purposes of anticipation. 413 F.3d 1326. That

is, a section 102 prior art reference does not have to be "effective" to be enabling and thus anticipating. Id. Under Rasmusson, the effectiveness of the prior art is not relevant. Id. Rather, the proper issue is whether the '940 patent is enabling in the sense that it describes the claimed invention sufficiently to enable a person of ordinary skill in the art to carry out the invention. As seen above, however, the district court focused only on the former question. Thus, we remand to allow the district court to make the proper factual determinations and then reach its own legal conclusion as to whether the '940 patent is enabled.

We reach a different conclusion, however, with respect to the '624 application. The '624 application does not identify riluzole by name. As found by the district court, riluzole is just one of hundreds of compounds included in formula I. When a reference discloses a class of compounds, i.e., a genus, a person of ordinary skill in the art should be able to "at once envisage each member of th[e] . . . class" for the individual compounds, i.e., species, to be enabled. In re Petering, 301 F.2d 676, 681 (C.C.P.A. 1962). If the members cannot be envisioned, the reference does not disclose the species and the reference is not enabling. Here, with the large number of compounds included in formula I and no specific identification of riluzole by the '624 application, the '624 application does not disclose riluzole, and therefore, cannot enable treatment of ALS with riluzole. The '624 application cannot anticipate any of claims 1-5 of the '814 patent.

In sum, we do not disturb the ruling of the district court that the '624 application does not anticipate. However, we vacate the ruling of the district court with respect to the '940 patent and remand the case to the district court for further proceedings. On

remand, the district court should determine whether the '940 patent is enabling, using the proper legal standard. That has not yet been done because, as seen, the district court stopped its analysis after concluding that the '940 patent did not disclose that the compounds of formula I were effective in treating ALS. What the district court must determine on remand is whether the disclosure of formula I in the '940 patent enables a person of ordinary skill in the art to carry out the invention claimed in claims 1-5 of the '814 patent. See Elan Pharms., 346 F.3d at 1057. Specifically, the district court must determine whether the '940 patent enables a person of ordinary skill in the art to treat ALS with riluzole. Effectiveness in treating ALS does not have to be established. See Rasmusson, 413 F.3d at 1325-26. If the district court determines that what is disclosed in formula I of the '940 patent is enabling in that a person of ordinary skill in the art can carry out the invention, then it will be for the district court to determine whether that disclosure anticipates claims 1-5 of the '814 patent. If, however, the district court determines that what is disclosed in formula I of the '940 patent is not enabling in that a person of ordinary skill in the art could not carry out the invention, then the district court should again hold that claims 1-5 of the '814 patent are not anticipated by the disclosure of the '940 patent and that therefore claims 1-5 are not invalid.

CONCLUSION

In sum,

(1) We affirm the district court's determination that there was no inequitable conduct.

(2) We vacate the district court's determination that claims 1-5 of the '814 patent are not invalid by reason of anticipation. We remand the case to the district court for further proceedings consistent with this opinion, as set forth above.

COSTS

Each party shall bear its own costs.

AFFIRMED-IN-PART, VACATED-IN-PART, and REMANDED

United States Court of Appeals for the Federal Circuit

05-1313

IMPAX LABORATORIES, INC.,

Plaintiff-Appellant,

v.

AVENTIS PHARMACEUTICALS INC.,

Defendant-Appellee.

RADER, Circuit Judge, concurring in part.

I join the majority opinion on all points except the anticipation determination. Examining the record in this case, I think the district court did make a proper finding regarding anticipation. Therefore, in my view, the case does not require a remand. This court's opinion states that the reason the district court determined that the '814 patent was not anticipated by the '940 patent was because "the [district] court apparently determined that even though formula I of the '940 patent disclosed riluzole, the formula did not anticipate the '814 patent because it did not disclose riluzole as being effective for treating ALS." Majority Opinion, 22. Thus, citing Rasmussen v. SmithKline Beecham Corp., 766 F.2d 531, 533 (Fed. Cir. 1985), the majority opinion remands because a "reference need not demonstrate utility" for anticipation. Majority Opinion, 25.

While the trial court referred to effectiveness, its findings go beyond that narrow ruling and suffice to uphold its judgment. For example, the district court noted first that formula I encompasses a particularly large number of compounds. Impax Labs., Inc. v. Aventis Pharms., Inc., 333 F. Supp. 2d 265, 271-72 (D. Del.

2004). In addition, the district court examined the specification of the '940 patent and determined that riluzole was not meaningfully discussed in the treatment of medical conditions associated with the effects of glutamate. Id. at 272. Moreover, the court determined that the language of the '940 patent itself created "substantial uncertainty" regarding use of glutamate inhibiting compounds in the treatment of ALS. Id. The court determined that the language in the patent discussing conditions implicating glutamate to be speculative, at best. Id. Thus, I read the district court to have found that the '940 disclosure did not put one of skill in the art in possession of the invention at all. Elan Pharms., Inc. v. Mayo Found., 346 F.3d 1051, 1057 (Fed. Cir. 2003). When it found that the disclosure leaves "substantial uncertainty," the trial court sufficiently supported its holding. Id. The '940 disclosure does not make it a potential treatment in any way.

Further, the majority opinion provides even more evidence that the '940 patent is not an enabling reference for the purposes of anticipating the '814 patent. For example, the opinion notes that the '940 patent was considered by the examiner during prosecution and not considered a prior art reference to support a rejection of the claims. Majority Opinion, 23. In addition, the opinion points out that Impax's own expert "was unable to identify any specific teaching in the '940 patent that would have led one to riluzole." Id. Further, Aventis' expert found that the disclosure of the '940 patent would not have given a person a reasonable expectation of success in treating ALS. Id. at 24. Once again, the record – even beyond the parts cited by the trial judge – show no anticipation.

Anticipation does not require proof of "utility," or (in other words) "actual performance of suggestions in a disclosure," Bristol-Myers Squibb Co. v. Ben Venue Labs., 246 F.3d 1368, 1378 (Fed. Cir. 2001), but in this case, the district court has found that the disclosure does not make even a suggestion of disclosure to one of skill in the art. Beyond the efficacy question, the '940 patent does not even disclose the necessary suggestion to enable one of ordinary skill in the art to look to riluzole for the treatment of ALS in the first place. Thus, I would affirm the district court's determination of anticipation without requiring a remand in this case.