United States Court of Appeals for the Federal Circuit

2009-1350

ALZA CORPORATION
and MCNEIL-PPC, INC.,

Plaintiffs-Appellants,

v.

ANDRX PHARMACEUTICALS, LLC
and ANDRX CORPORATION,

Defendants-Appellees.

Constantine L. Trela, Jr., Sidley Austin LLP, of Chicago, Illinois, argued for plaintiffs-appellants. With him on the brief were David T. Pritikin; Jeffrey P. Kushan, Todd A. Wagner and Peter S. Choi, of Washington, DC.

C. Kyle Musgrove, Kenyon & Kenyon LLP, of Washington, DC, argued for defendants-appellees. With him on the brief were John W. Bateman and Robert F. Vroom.

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

2009-1350

ALZA CORPORATION
and MCNEIL-PPC, INC.,

Plaintiffs-Appellants,

v.

ANDRX PHARMACEUTICALS, LLC
and ANDRX CORPORATION,

Defendants-Appellees.

Appeal from the United States District Court for the District of Delaware in case no. 05-CV-642, Judge Joseph J. Farnan, Jr.

DECIDED: April 26, 2010

Before DYK, SCHALL, and PROST, Circuit Judges.

PROST, Circuit Judge.

ALZA Corporation and McNeil-PPC, Inc. (collectively, "ALZA") appeal from a final decision of the United States District Court for the District of Delaware. Following a bench trial, the district court found the patented treatment methods of U.S. Patent No. 6,919,373 ("'373 patent") nonobvious, but held the asserted claim both not infringed and invalid for lack of enablement. We affirm because we conclude that the asserted claims of the '373 patent are invalid for lack of enablement.

BACKGROUND

The '373 patent claims methods for treating primarily Attention Deficit and Hyperactivity Disorder ("ADHD") through a methylphenidate ("MPH") drug dosage form

that has an ascending release rate over an extended period of time. The '373 patent application, filed in 1999, claimed priority to provisional application No. 60/031,741 ("'741 application"), filed on November 25, 1996, and the earliest non-provisional application No. 08/910,593 ("'593 application"), filed on July 31, 1997.

Before the claimed invention, ADHD had been treated with other oral drugs, the most common of which, Ritalin®, was an immediate-release ("IR") formulation of MPH. This formulation releases the drug within minutes and treats the symptoms for three to five hours. As a result, such prior drug treatments were taken two or three times a day. As many patients who take ADHD medication are children, they took one dose before school and one or two additional doses about four to five hours apart, at least one of which was administered at school. Thus, a once-a-day method of treating ADHD offered the potential of reducing patient-compliance problems that resulted from the need for treatment during the school day.

At the time of the invention, it was well known how to develop sustained-release dosage forms, also known as "controlled release" or "extended release." Designed to release the drug at a constant rate, sustained-release dosage forms typically provided the desired steady therapeutic effect. It was also known that sustained-release dosage forms could exhibit descending or ascending release rates by manipulating the methods and materials used to produce the dosage forms.

After a series of clinical studies, ALZA determined that MPH plasma concentrations that had ascending patterns provided greater efficacy for treating ADHD than concentrations that were constant. Using this knowledge, ALZA developed safe and effective once-a-day extended release oral dosage forms that could deliver MPH

with the ascending release pattern. Admittedly, the bulk of ALZA's efforts went into developing an osmotic dosage form, which uses a compartment containing drug and various osmotic excipients.

ALZA subsequently filed its patent applications. Claim 1, the only independent claim implicated on appeal, of the '373 patent claims:

> A method for treating ADD or ADHD comprising administering a dosage form comprising methylphenidate that provides a release of methylphenidate at an ascending release rate over an extended period of time.

'373 patent col.23 ll.12–15 (emphasis added). The specification focuses on how osmotic systems can be adapted to create an ascending release dosage form to treat ADHD. The specification also mentions non-osmotic dosage forms. Id. at col.3 ll.53–62.[1]

ALZA markets and sells a product called CONCERTA®, which embodies the claimed invention; upon ingestion, it releases the drug at an ascending rate for an extended period of time, as required by claim 1. ALZA's competitors, Andrx Pharmaceuticals, LLC and Andrx Corporation (collectively, "Andrx"), produce a product pursuant to an approved Abbreviated New Drug Application ("ANDA"). Like

[1] Osmotic dosage forms are dosages with a "push" layer comprising osmotically effective solutes—i.e., substances that dissolve and, as fluid is imbibed through the semipermeable pill wall, swell and push against the deliverable drug formulation. The pill wall is semipermeable, meaning that it is permeable to the passage of external fluids into the compartment, but is substantially impermeable to the passage of a drug agent or excipients outward. The drug itself exits via an orifice, which constitutes the "passageway" through the wall for delivering the drug from the pill, so as to gradually increase drug concentration in the body.

Non-osmotic dosage forms within the scope of the claims include "oral tablets and capsules" with sustained-release dosage forms suitable for producing ascending release rates, where the release rate is as determined by an appropriate in-vitro dissolution test. Non-osmotic dosage forms do not have a "push" layer.

CONCERTA®, Andrx's product has an outer IR coating around a sustained-release inner core. In 2005, ALZA sued Andrx, alleging infringement of the '373 patent and U.S. Patent No. 6,930,129 ("'129 patent").[2] Andrx denied that its products infringed the patents. It also asserted affirmative defenses, alleging that the '373 patent was invalid because it was obvious and not enabled, and counterclaimed for a declaratory judgment of noninfringement and invalidity of the asserted claims of the '373 patent.

The district court held a Markman hearing on the construction of various terms in dispute. In rejecting Andrx's attempt to limit the scope of the claim to osmotic dosage forms, the court construed the phrases "pharmaceutically acceptable composition" and "dosage form" to mean "a pharmaceutical composition that includes a dose of methylphenidate," which includes non-osmotic dosage forms, as ALZA requested.[3] Alza Corp. v. Andrx Pharms., LLC, No. 05-642, at 2 (D. Del. Oct. 5, 2007) (order on claim construction). Further, the court construed the disputed term "an ascending release rate over an extended period of time" to mean:

> a release of methylphenidate from the dosage form wherein the amount released in a periodic interval is increased over the amount released during the immediately preceding periodic, interval starting at t=0 and continuing through at least the mid-point of the T90 and for at least three hours. The release rate is determined by an appropriate in-vitro dissolution test. The ascending release rate does not include release of

[2] On the first day of the bench trial, ALZA moved to dismiss its claims relating to the '129 patent with prejudice. J.A. 12535. The district court dismissed Andrx's declaratory judgment counterclaims regarding the '129 patent without prejudice for lack of jurisdiction. Alza Corp. v. Andrx Pharms., LLC, 607 F. Supp. 2d 614, 624 (D. Del. 2008). The '129 patent is therefore not at issue in this appeal.

[3] Neither party challenges the district court's finding that claim 1 includes both osmotic and non-osmotic dosage forms.

> drug from any immediate-release drug coating that may be applied to the dosage form.[4]

Id.

Following a bench trial, the district court determined that the '373 patent was not infringed. The district court concluded that claim 1, as construed, "require[s] release of non-IR MPH during the initial interval of an appropriate dissolution test." Alza, 607 F. Supp. 2d at 624. According to the district court, there was substantial evidence that "the amount of [MPH] released [by Andrx's product] in the first hour of the dissolution test is all attributable to the IR portion of methylphenidate," which ALZA failed to adequately rebut. Id. at 628–31. The district court also found the asserted claims of the '373 patent not obvious.

The district court, however, concluded that the asserted claims are invalid for lack of enablement because the specification does not enable the full scope of claim 1, which covers both osmotic and non-osmotic dosage forms. Before the district court, the parties agreed that the specification enables osmotic oral dosage forms, but disputed whether it also enables non-osmotic oral dosage forms. While the court found that the claim includes non-oral as well as oral dosage forms, it concluded that it could resolve the enablement dispute between the parties in Andrx's favor solely by looking to non-osmotic oral tablets and capsules. As a result, it explained that the enablement issue reduces to factual considerations with regard to whether undue experimentation is required to make oral dosage forms other than osmotic dosage forms that meet the limitations of the claims. Applying the factors set forth in In re Wands, 858 F.2d 731,

[4] Before the district court and on appeal, the parties dispute whether the inner core, which releases MPH over an extended time period, infringes the '373 patent.

735 (Fed. Cir. 1988),[5] the district court found that developing non-osmotic oral dosage forms, such as tablets and capsules, as claimed requires undue experimentation. Alza, 607 F. Supp. 2d at 651–59. Accordingly, the district court determined that the asserted claims are not enabled and thus invalid.

ALZA timely appeals. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

On appeal, ALZA argues that the district court erred in finding claim 1 invalid for lack of enablement. The parties agree that the claim construction adopted by the district court requires the enablement of both osmotic and non-osmotic dosage forms and they also agree that osmotic dosage forms are enabled. The dispute is whether the specification would have enabled a person of ordinary skill in the art to create non-osmotic oral dosage forms—namely, tablets and capsules—with ascending release rates without undue experimentation at the time of filing.[6]

ALZA asserts that creating non-osmotic dosage forms and manipulating their release rates was well known to a person of ordinary skill in the art at the time the '373 patent application was filed. In addition, ALZA argues that the specification provides sufficient guidance regarding non-osmotic dosage forms because it identifies a variety

[5] The factors 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." Wands, 858 F.2d at 737.

[6] ALZA also argues that the claimed non-osmotic dosage forms should be limited to oral dosage forms and exclude non-oral dosage forms. We need not resolve this issue, however, because we agree with the district court that non-osmotic oral dosage forms are not enabled.

of suitable non-osmotic dosage forms and cites to a portion of a standard text to explain how to make and use such non-osmotic, sustained-release dosage forms with experimentation. ALZA concedes that even with the guidance provided in the specification, a person of ordinary skill in the art would be required to engage in an iterative, trial-and-error process to practice the claimed invention; however, it disputes that the amount of experimentation required is undue. Instead, ALZA argues that non-osmotic dosage forms with ascending release rates could be made with only routine effort by those skilled in the art because the methods and materials used to produce dosage forms with constant, descending, or ascending release rate profiles are essentially the same and well known.

Andrx disputes ALZA's contention that enablement can be satisfied by referring to what persons of ordinary skill would know because what one of the proper skill in the art knows cannot substitute for disclosure of novel aspects of the invention, i.e., the non-osmotic dosage forms exhibiting ascending release rates. Further, Andrx argues that the evidence presented at trial indicates that even one skilled in the art would find it difficult to develop a non-osmotic dosage form exhibiting an ascending release rate, particularly in light of the sparse guidance provided in the specification. Andrx asserts that the district court's factual findings that making a non-osmotic dosage form would require undue experimentation were not clearly erroneous, but rather, supported by the record. Andrx points to three Wands factors in particular—the guidance provided by the specification, the presence or absence of working embodiments, and the breadth of the claims—and submits that they strongly weigh in favor of a finding that creating non-osmotic dosage forms with ascending release rates requires undue experimentation.

Upon review of the record, we agree with Andrx that the district court was correct in concluding that the asserted claims are invalid for lack of enabling non-osmotic oral dosage forms with ascending release rates.

We begin with the statute. The enablement requirement is codified in 35 U.S.C. § 112, ¶ 1, which 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, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement is determined as of the effective filing date of the patent's application. See Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1371–72 (Fed. Cir. 1999). "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). "Whether undue experimentation would have been required to make and use an invention, and thus whether a disclosure is enabling under 35 U.S.C. § 112, ¶ 1, is a question of law that we review de novo, based on underlying factual inquiries that we review for clear error." See Enzo Biochem, 188 F.3d at 1369. Because patents are presumed valid, lack of enablement must be proven by clear and convincing evidence. See Auto. Tech. Int'l, Inc. v. BMW of N. Am., Inc., 501 F.3d 1274, 1281 (Fed. Cir. 2007); AK Steel Corp. v. Sollac & Ugine, 344 F.3d 1234, 1238–39 (Fed. Cir. 2003). The district court's determination of the hypothetical person of ordinary skill in the relevant art is a finding of fact we review for

clear error. Graham v. John Deere Co. of Kan. City, 383 U.S. 1, 17 (1966); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379–80 (Fed. Cir. 1986).

Enablement is not precluded where a "reasonable" amount of routine experimentation is required to practice a claimed invention, however, such experimentation must not be "undue." Enzo Biochem, 188 F.3d at 1371; Wands, 858 F.2d at 736–37. In Wands, we set forth the following factors that a court may consider when determining if a disclosure requires undue experimentation:

> (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.

858 F.2d at 737. We explained that "[w]hether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." Id. The district court found that seven of the eight Wands factors weighed in favor of a finding that undue experimentation would be required to enable the full scope of the claims. ALZA fails to demonstrate that the court's factual findings in this regard are clearly erroneous. We conclude that they are not.

We agree first with the district court that the specification of the '373 patent only describes osmotic dosage forms and does not provide sufficient guidance for a person of ordinary skill in the art to make the non-osmotic dosage forms as claimed. To the extent that ALZA argues that the knowledge of a person of ordinary skill in the art satisfies the enablement requirement, we disagree. As this court has repeatedly stated, "the rule that a specification need not disclose what is well known in the art is 'merely a rule of supplementation, not a substitute for a basic enabling disclosure.'" Auto. Tech.,

501 F.3d at 1282 (quoting Genentech, 108 F.3d at 1366). To satisfy the plain language of § 112, ¶ 1, ALZA was required to provide an adequate enabling disclosure in the specification; it cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification.

In arguing that the disclosure in the '373 patent specification does enable a person of ordinary skill to make and use the claimed dosage forms, ALZA directs us to ten lines of the specification, which mention non-osmotics and refer to a textbook discussing how to make and use various types of non-osmotic sustained-release dosage forms. See '373 patent col.3 ll.53–62. The specification states:

> There are many approaches to achieving sustained release of drugs from oral dosage forms known in the art. These different approaches include, for example, diffusion systems such as reservoir devices and matrix devices, dissolution systems (including, for example, "tiny time pills") and matrix dissolution systems, combination diffusion/dissolution systems, osmotic systems and ion-exchange resin systems as described in Remington's Pharmaceutical Sciences, 1990 ed., pp. 1682-1685.

Id. We agree with the district court that this disclosure provides "no guidance as to how to achieve ascending release with non-osmotic oral dosage forms." Alza, 607 F. Supp. 2d at 655. The "omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the condition under which a process can be carried out, undue experimentation is required." Auto. Tech., 501 F.3d at 1283–84 (quoting Genentech, 108 F.3d at 1366).

The specification here does not contain "such full, clear, concise, and exact terms as to enable any person skilled in the art" to make and use non-osmotic oral dosage forms with ascending release rates. 35 U.S.C. § 112, ¶ 1. Instead, it provides

"only a starting point, a direction for further research." Auto. Tech., 501 F.3d at 1284; Genentech, 108 F.3d at 1366. Indeed, even ALZA concedes that a person of ordinary skill in the art would have been required to engage in an iterative, trial-and-error process to practice the claimed invention even with the help of the '373 patent specification. Thus, we agree with the district court that resolving the enablement issue in this case rests on the underlying factual findings regarding whether undue experimentation is required to make non-osmotic oral dosage forms with ascending release rates.

Despite ALZA's assertions, we find no clear error in the district court's finding that the field of ascending release dosage forms was not mature at the time the '373 patent was filed and was a "breakaway" from the prior art, and thus, the preparation of such dosage forms was not routine. Alza, 607 F. Supp. 2d at 652. These findings are supported by the '373 patent specification and prosecution history, and bolstered by witness testimony.

In its challenge to the district court's findings, ALZA relies heavily on the testimony of its expert witness Dr. Martyn Davies, who explained that the experimentation required here is merely routine. The district court gave little weight to Dr. Davies's testimony in this regard in light of contradictory testimony from other witnesses. There is at least one problem with Dr. Davies's testimony, and that is that the level of skill in the art upon which he based his analysis is a higher level of skill than the one the court adopted.[7] Dr. Davies did not contend that the specification would

[7] While ALZA also challenges the district court's determination of the level of skill in the art on appeal, we find no clear error.

enable a person at the level of skill that the court adopted. Accordingly, we conclude that the court did not clearly err in giving less weight to this testimony.

ALZA also challenges the district court's reliance on the testimony of two of ALZA's own employees, Andrew Lam and Lawrence Hamel, who explained that despite its efforts, ALZA had been unable to develop these purported "routine" non-osmotic dosage forms exhibiting ascending release rates and that even development of the osmotic form had been difficult. Specifically, ALZA argues that the district court's reliance on Lam's testimony was misplaced because he is not skilled in the art and at best testified that "trial-and-error" experimentation is required. ALZA also argues that reliance on Hamel's testimony was improper because it is irrelevant since it related only to the difficulties in developing the osmotic form. We disagree because Lam's and Hamel's level of skill in the art does not affect their knowledge relating to ALZA's difficulties in creating a non-osmotic dosage form as claimed, which was relevant to ALZA's arguments that the quantity of experimentation required was not undue. At trial, ALZA argued that it did produce non-osmotic dosage forms with ascending release profiles, offering the testimony of its scientist Atul Ayer for support. When Ayer could not corroborate his statements, however, the district court found that Ayer's testimony actually cut against ALZA's assertions that the preparation of such dosage forms was a routine matter. Although ALZA complains that this consideration improperly shifted Andrx's burden on it, we disagree. This evidence merely contradicts its own witnesses'

testimony that such development was routine, easily made by those skilled in the art, and created by ALZA.[8]

We find no clear error in the district court crediting the testimony of Lam over Dr. Davies and Ayer, and concluding that "ALZA had in fact tried and failed for a few months to produce non-osmotic ascending release dosage forms." Alza, 607 F. Supp. 2d at 653. The district court addressed the arguments that ALZA continues to make on appeal in making credibility determinations and factual findings that ALZA was unable to create non-osmotic dosage form with an ascending release rate and without undue experimentation. We conclude that the district court did not clearly err in giving weight to this testimony when finding that the quantity of experimentation required to practice the claimed invention was undue based on the record as a whole.

Accordingly, ALZA has failed to demonstrate that the district court clearly erred in the underlying factual findings on which the Wands factors are based. Rather, the Wands factors weigh in favor of finding that the experimentation required to practice part of the claimed invention was not routine. "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." Genentech, 108 F.3d at 1366 (citing Brenner v. Manson,

[8] ALZA complains that the district court's reliance on the "conclusory" testimony of Andrx's expert, Dr. Thomas Needham, further confirms that the court improperly reversed the burden of proof. We find that the district court did not clearly err in crediting the testimony of Dr. Needham, whose analysis was based on the level of skill in the art that the court adopted. Dr. Needham stated that based on the lack of guidance in the specification, a person of skill would need to engage in a great deal of experimentation (six months or more) to develop a single, non-osmotic dosage form. J.A. 12719. Dr. Needham also testified that based on the disclosure in the specification, creating osmotic dosage forms would require one month of testing. Id. ALZA fails to show that the court improperly shifted the burden of proof to ALZA or clearly erred in relying on this testimony when weighing the Wands factors.

383 U.S. 519, 536 (1966)). Here, the evidence dictates that a person of ordinary skill in the art would have been required to engage in undue experimentation to develop non-osmotic oral dosage forms with ascending release rates.

As we stated in Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371 (Fed. Cir. 2007), and repeated in Automobile Technologies, "The irony of this situation is that Liebel successfully pressed to have its claims include a jacketless system, but, having won that battle, it then had to show that such a claim was fully enabled, a challenge it could not meet." Auto. Tech. 501 F.3d at 1285 (quoting Liebel-Flarsheim, 481 F.3d at 1380). In this case, ALZA successfully argued to the district court that the claims encompassed both osmotic and non-osmotic dosage forms. However, ALZA's patent specification does not enable the full scope of the claims, namely non-osmotic oral dosage forms with ascending release rates. Rather, the clear and convincing evidence based on the quantity of experimentation, lack of guidance in the specification, absence of working embodiments, and breadth of the claims demonstrates that the '373 patent specification fails to enable a person of ordinary skill to make and use non-osmotic oral dosage forms with ascending release rates. Therefore, the asserted claims fail to meet the enablement requirement. See Auto. Tech., 501 F.3d at 1285.

We conclude that the asserted claims are invalid for lack of enablement under 35 U.S.C. § 112, ¶ 1. We need not address ALZA's argument that the court erred in its claim construction with respect to whether the claims require that the dosage form administered in the claimed treatment release some drug during the first periodic interval and thus in its finding of noninfringement, because the claims would be invalid

under any reasonable construction. Further, we need not reach Andrx's argument that in the alternative the claims are invalid as obvious under 35 U.S.C. § 103.

CONCLUSION

For the reasons set forth above, we affirm the district court's determination that the asserted claims are invalid for lack of enablement.

AFFIRMED