NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

2008-1549, -1550

ORTHO-MCNEIL PHARMACEUTICAL, INC.,

Plaintiff-Appellant,

v.

TEVA PHARMACEUTICALS INDUSTRIES, LTD.,
TEVA PHARMACEUTICALS USA, INC., and WATSON LABORATORIES, INC.,

Defendants-Appellees,

and

KALI LABORATORIES, INC., PAR PHARMACEUTICAL COMPANIES, INC.,
and PAR PHARMACEUTICAL, INC.,

Defendants,

and

CARACO PHARMACEUTICAL LABORATORIES, LTD.,

Defendant-Appellee.

Constantine L. Trela, Jr., Sidley Austin LLP, of Chicago, Illinois, argued for plaintiff-appellant. With him on the brief were David T. Pritikin, Lisa A. Schneider and Linda R. Friedlieb. Of counsel on the brief were Jeffrey P. Kushan, of Washington, DC, and Michael D. Hatcher, of Dallas, Texas.

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Steven E. Feldman, Husch Blackwell Sanders Welsh & Katz, of Chicago, Illinois, for amicus curiae Apotex, Inc. With him on the brief was Sherry L. Rollo.

Appealed from: United States District Court for the District of New Jersey

Judge Dennis M. Cavanaugh

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Defendant-Appellee.

Appeals from the United States District court for the District of New Jersey in case nos. 04-CV-886 and 06-CV-3533, Judge Dennis M. Cavanaugh.

DECIDED: August 26, 2009

Before MAYER, PROST, and MOORE, Circuit Judges.

Opinion for the court filed by Circuit Judge PROST. Dissenting opinion filed by Circuit Judge MAYER.

PROST, Circuit Judge.

INTRODUCTION

This case is a patent law appeal from a district court order granting summary judgment of invalidity based on anticipation and obviousness. Ortho-McNeil Pharmaceutical ("Ortho") brought suit against Teva Pharmaceuticals Industries ("Teva") and Caraco Pharmaceutical Laboratories ("Caraco") alleging infringement of U.S. Reissued Patent 39,221 ("RE'221"), directed to a combination tramadol and acetaminophen composition for use in prescription pain relief. We vacate-in-part, affim-in-part, and remand.

Acetaminophen is a popular non-opioid pain reliever, more commonly known by the brand name Tylenol®. Acetaminophen has a poorly understood mechanism of action, and interacts with other drugs in ways that could not be predicted in 1990. Nonetheless, it was a popular pain reliever and Ortho had a history of experimenting with combining acetaminophen and other drugs.

Tramadol is an atypical weak opioid with an unclear mechanism of action. Tramadol and methods of making and using it were first described in U.S. Patent No. 3,652,589 to Flick. Flick mentions that tramadol can be combined with other analgesics, and often exhibits synergistic effects. The specification of Flick also includes 23 working examples. The first 22 examples describe different tramadol formulations. Example 23 discloses a combination of tramadol, p-acetamino-phenol, pentobarbital sodium, and ethoxy benzamide. In 1990, Tramadol was known to have several serious side effects, and for that reason was commonly administered through gradual dose titration.

Ortho first claimed a combination tramadol and acetaminophen tablet in 1990, in U.S. Patent No. 5,336,691 ("'691 patent"). The patent described one benefit of the claimed composition as a synergistic effect between tramadol and acetaminophen. Ortho received FDA approval for such a combination tablet and marketed its product as Ultracet®. Ultracet® immediately became the fastest growing prescription pain reliever and enjoyed considerable commercial success. Several generic drug companies filed abbreviated new drug applications ("ANDAs") to market generic versions of Ultracet®. Ortho brought multiple different lawsuits against these companies asserting the '691 patent against the ANDAs.

In pretrial motions, several of the drug companies alleged that the '691 patent was invalid for anticipation and obviousness based on Flick and other references. During the course of litigation, Ortho discovered that the p-acetamino-phenol mentioned in the Flick patent was actually an archaic name for acetaminophen. The ratio of tramadol to p-acetamino-phenol in the four-compound combination of Flick's example 23 is 1:10, which falls within the scope of some of the claims of the '691 patent. In light of the cited references and the fact that p-acetamino-phenol is acetaminophen, Ortho sought reexamination and reissue of the '691 patent. Ortho submitted to the examiner the relevant prior art, a summary judgment motion submitted by Kali Laboratories, and a letter submitted by Barr Pharmaceuticals arguing anticipation and obviousness of the '691 patent.

Other prior art cited to the examiner during reissue proceedings and to the district court includes a series of German publications based on the WHO Cancer Pain Guidelines (hereinafter "the German references"). Collectively, these articles teach a

method of managing cancer pain using a ladder approach aimed at customizing a co-administration of pain relievers and dosing regimens to meet the needs of each patient. The strengths of the medications and the dosages increase as the prescriber moves up the ladder. The middle rung of the ladder includes a non-opioid analgesic co-administered with a weak opioid. None of the German references mentions synergy.

In reissue proceedings for the '691 patent, Ortho canceled all but one of the asserted claims and redrafted them to narrow the scope of the invention and attempt to avoid the cited prior art references. Ortho also argued to the examiner that one of ordinary skill in the art at the time of filing would not understand the prior art to disclose the claimed invention as amended. The examiner ultimately allowed several redrafted claims and the one previously allowed claim to reissue as RE'221.

While the reissue proceedings were pending, Teva and Caraco filed summary judgment motions for invalidity and non-infringement of claim 6 of the '691 patent. Claim 6 was the one original claim allowed in RE'221, amended to independent form. Ortho then amended its complaints to assert the new reissue claims as well as RE'221 claim 6 against Teva and Caraco (among others) in the ongoing ANDA litigation between the parties. Ortho's cases against Teva and Caraco were then consolidated.

Teva and Caraco filed summary judgment motions for invalidity and non-infringement, asserting that RE'221 was anticipated and rendered obvious by Flick and the German references. Ortho disputed Teva's and Caraco's interpretations of the prior art disclosures and submitted uncontroverted expert testimony explaining that one of skill in the art at the time of the original filing would not understand Flick, or the German references to disclose or render obvious the claimed invention.

On August 12, 2008, the district court granted summary judgment invalidating RE'221 claims 43-48, 51, 54, 67, 69, 72, and 74 as obvious over the prior art, and invalidating claim 6 as anticipated and obvious over the prior art.[1] Ortho-McNeil timely filed its notice of appeal on August 25, 2008. This court has jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

This court reviews a grant of summary judgment de novo. Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1302 (Fed. Cir. 2005). Obviousness is ultimately a determination of law, though it is based on questions of fact. Id. at 1302. Anticipation is a question of fact. Id. Because issued patents enjoy a presumption of validity, obviousness and anticipation must be proven by clear and convincing evidence. Impax Labs., Inc. v. Aventis Pharma., Inc., 545 F.3d 1312, 1314 (Fed. Cir. 2008). When the patent examiner has considered the asserted prior art and basis for the validity challenge during prosecution, the burden of proving invalidity is especially heavy. Id.; Hewlett-Packard Co. v. Bausch & Lomb Inc., 909 F.2d 1464, 1467 (Fed. Cir. 1990). Summary judgment is only appropriate where there are no material questions of fact and the movant is entitled to judgment as a matter of law. Celotex Corp. v. Catrett, 477 U.S. 317, 322-23 (1986); Fed. R. Civ. P. 56(c).

Inventions in most instances rely upon building blocks long since uncovered, and combine elements that are in some sense already known. KSR Int'l Co. v. Teleflex,

[1] The district court identified the asserted claims as 43-47, 51, 67, and 69, although both parties identified the asserted claims as 43-48, 51, 54, 67, 69, 72, and 74. We will assume that the district court intended to grant the defendants' summary judgment motion with respect to all of the asserted claims and not solely the ones listed by the court in its opinion.

Inc., 550 U.S. 398, 418-19 (2007). The combination of familiar elements according to known methods is likely to be obvious, however, when it does no more than yield predictable results. Id. at 1739. Each case must be decided in its particular context, including the characteristics of the science or technology, the nature of the choices available to one skilled in the art, the specificity of the prior art, and the predictability of results in the area of interest. Abbott Labs. v. Sandoz, Inc., 544 F.3d 1341, 1352 (Fed. Cir. 2008).

I. Validity of the Reissue Claims

Each of claims 43-48, 51, 54, 67, 69, 72, and 74 recites a pharmaceutical composition with active ingredients consisting of tramadol and acetaminophen in a ratio of about 1:5 to about 1:19. A single tablet containing only tramadol and acetaminophen in a fixed dose ratio within the claimed range is not disclosed in the cited prior art. Flick discloses a four-compound combination comprising tramadol, acetaminophen, and two other active ingredients. Flick does not suggest that the pentobarbital sodium and ethoxy benzamide are merely optional for the combination to work as desired. The parties dispute whether Flick suggests that the composition in example 23 exhibits a synergistic effect.

Ortho submitted uncontroverted expert testimony that one of ordinary skill in the art would not find it obvious to try to remove two of the four active ingredients disclosed in Flick example 23 to arrive at the claimed composition. The expert explained that drug interactions are complicated and unpredictable. He testified that the interactions of tramadol and acetaminophen were especially poorly understood in 1990. The expert testified that one of skill in the art would not expect the combination of solely tramadol

and acetaminophen to have any particular advantage unless Flick or some other reference specifically identified one. The expert testified that Flick's broad statement that tramadol "often" displays synergistic affects when combined with other analgesics would not be enough give one of ordinary skill any expectations whether tramadol combined only with acetaminophen in a 1:5 to 1:19 ratio would exhibit the synergistic effects discovered by Ortho.

Ortho's expert also testified that no combination of the German references and Flick would suggest the claimed combination of tramadol and acetaminophen. The expert explained that the German references actually teach away from the claimed composition because they emphasize the importance of flexibility in choosing combinations and doses of medications based on individual needs. The expert testified that the claimed fixed-dosage combination tablet was disparaged in the German references and disfavored in the art at the time.

Ortho's proffered reading of Flick and the German references, as well as expert testimony regarding the understanding of one skilled in the art, raises material questions of fact as to whether a skilled artisan would have found the claimed combination of tramadol and acetaminophen to be obvious. We therefore vacate the district court's summary judgment invalidating RE'221 claims 43-48, 51, 54, 67, 69, 72, and 74 based on obviousness and remand the case for a trial on the merits.

II. Validity of Claim 6

Claim 6 recites a composition comprising tramadol and acetaminophen in an about 1:5 ratio. Unlike the other reissue claims, the open transitional term "comprising" causes claim 6 to read on compositions that include active ingredients other than

tramadol and acetaminophen. Flick's example 23 thus differs from claim 6 only by the disclosed ratio of tramadol to acetaminophen (1:10 versus "about 1:5"). This court previously construed the claimed "about 1:5" ratio to read on a ratio from 1:3.6 to 1:7.1. Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs., Ltd., 476 F.3d 1321, 1328 (Fed. Cir. 2007).

The district court found that claim 6 was invalid for both anticipation and obviousness. We discuss each judgment in turn.

A

With respect to anticipation, Ortho contends that each element of claim 6 is not disclosed in Flick, and therefore is not anticipated. It is not disputed that example 23 of Flick discloses a pharmaceutical composition containing tramadol and acetaminophen, the first two limitations of claim 6. It is disputed whether example 6 discloses the claimed about 1:5 ratio, as that term is construed by this court.

The defendants argued to the district court that a paragraph at the end of example 22 teaches that tramadol can be administered in a 25 mg dose and that a preferred dose is 50 mg. Example 23 discloses 25 mg of tramadol in a four active agent combination. The defendants argue that these two teachings together suggest that the 25 mg dose of tramadol disclosed in example 23 can be modified to a 50 mg dose.

Ortho argued that example 22 discloses a tramadol-only formulation, and the suggestion to administer a 50 mg dose only applies to the administration of tramadol alone. Ortho argues that the specification does not teach increasing the dosage of tramadol past 25 mg when combining it with other active analgesics.

The district court agreed with the defendant's interpretation of Flick and found that examples 22 and 23 anticipate claim 6 when read in combination. The district court improperly resolved disputed questions of fact in reaching this conclusion. What a reference discloses is a question of fact. Para-Ordnance Mfg., Inc. v. SGS Imps. Int'l, Inc., 73 F.3d 1085, 1088 (Fed. Cir. 1995). The parties dispute whether and how Flick's teachings about varying dosages apply to example 23. The parties also dispute whether one of skill in the art would have understood the teachings of one working example to apply to a different working example. Whether Flick discloses all of the limitations of claim 6 is a material question of fact over which Ortho has raised a genuine dispute. We therefore vacate the district court's summary judgment that claim 6 is invalid for anticipation.

B

With respect to obviousness, there is no dispute that the only difference between claim 6 and example 23 of Flick is the weight ratio—the additional compounds in the example are irrelevant because of the transitional phrase "comprising" in the claim. Example 23 discloses a 1:10 ratio of tramadol to acetaminophen: 25 mg to 250 mg. Because the difference between 1:7.1 and 1:10 is so slight, Flick creates a prima facie case of obviousness with regard to claim 6. See Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 782-83 (Fed. Cir. 1985) ("The proportions are so close that prima facie one skilled in the art would have expected them to have the same properties."); Haynes Int'l, Inc. v. Jessop Steel Co., 8 F.3d 1573, 1577 n.3 (Fed. Cir. 1993) ("[W]hen the difference between the claimed invention and the prior art is the range or value of a

particular variable, then a prima facie rejection is properly established when the difference in range or value is minor.").

Ortho-McNeil can rebut the prima facie case if it can show that the prior art teaches away from the claimed range, or the claimed range produces new and unexpected results over the prior art range. See Iron Grip Barbell Co. v. USA Sports, Inc., 392 F.3d 1317, 1322 (Fed. Cir. 2004). Before the United States Patent and Trademark Office, the district court, and now us, Ortho-McNeil principally relies on unexpected results in the form of synergy between tramadol and acetaminophen. As described in RE'221, the observed analgesic effect of tramadol-acetaminophen combinations exceeds what one would predict from merely adding the effects observed upon administering each drug individually. See, e.g., RE'221 fig. 1. Ortho-McNeil's problem, however, is that its own evidence indicates no perceptible difference in synergy between a weight ratio of 1:7.1 and 1:10—and indeed over a much broader range of ratios. Id. Ortho-McNeil does not dispute this. Thus, Ortho-McNeil has failed to create a material dispute of fact regarding whether "the claimed range achieves unexpected results relative to the prior art range." In re Woodruff, 919 F.2d 1575, 1578 (Fed. Cir. 1990) (emphasis added); cf. Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1311-12 (Fed. Cir. 2006) ("Evidence of commercial success, or other secondary considerations, is only significant if there is a nexus between the claimed invention and the commercial success.").

Ortho-McNeil also relies on the declaration of Dr. Stanski, which asserts that

Flick teaches away from a ratio of about 1:5.[2] Dr. Stanski averred that one of ordinary skill would not have increased the amount of tramadol in Flick's example 23 because of concerns about the side effects of tramadol. However, Flick discloses higher doses than the 25 mg of example 23, including "preferably" tramadol-only formulations in doses of 50 mg and 75 mg, with no reservations about safety. See RE'221 col.12 ll.24-31. Setting that aside, and accepting Dr. Stanski's statement as true, it is nonetheless insufficient to rebut the prima facie case. The question is not whether Flick teaches away from increasing the amount of tramadol; the question is whether Flick teaches away from lowering the ratio of tramadol to acetaminophen from 1:10 to 1:7.1. This could be accomplished by increasing the amount of tramadol, which Dr. Stanski disparages, but it could equally be accomplished by decreasing the amount of acetaminophen. Dr. Stanski did not opine on that option, and therefore did not create a material issue of fact regarding whether the prior art teaches away from the claimed invention. We have considered Ortho's other arguments and find them to be without merit.

For these reasons, we agree with the district court that Ortho has failed to raise a genuine dispute of material fact regarding the obviousness of claim 6.

CONCLUSION

We vacate the district court's summary judgment order invalidating RE'221 claims 43-48, 51, 54, 67, 69, 72, and 74 based on obvious. We remand the case to the

[2] We confine our analysis to Dr. Stanski's August 25, 2005 declaration, as the supplemental expert testimony (submitted by Ortho when it was arguing the validity of the reissue claims) was not before the district court when determined that no material factual dispute existed regarding the obviousness of claim 6.

district court for proceedings consistent with this opinion. We vacate the district court's summary judgment invalidating RE'221 claim 6 based on anticipation. We affirm the district court's summary judgment invalidating claim 6 based on obviousness.

COSTS

Each party shall bear its own costs.

NOTE: This disposition is nonprecedential.

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MAYER, Circuit Judge, dissenting.

The claimed invention does nothing more than combine two well-known pain relievers—acetaminophen and tramadol—in a single tablet. Since the prior art clearly and unequivocally taught that these two analgesics could be combined for effective pain relief, the claimed invention is the epitome of obviousness. I therefore respectfully dissent.

Ortho-McNeil Pharmaceutical, Inc. ("Ortho") did not invent acetaminophen and it did not invent tramadol. Long before the critical date for U.S. Patent No. RE39,221 (the "RE221 patent"), acetaminophen had been combined with other pain relievers, including opioid pain medications such as tramadol. Such compositions include Tylenol® with Codeine, Tylox® (acetaminophen with oxycodone), and Vicodin® (acetaminophen with hydrocone bitartrate). Prior to the effective date of the RE221 patent, it was widely recognized that the combination of a peripherally-acting non-opioid analgesic, such as acetaminophen, and a centrally-acting opioid analgesic, such as tramadol, was an effective way to treat pain that did not respond to the use of non-opioid pain relievers alone.

In fact, a patent issued in 1972 specifically discloses the use of tramadol in combination drugs including phenacetin—which metabolizes into acetaminophen in the human body—to achieve synergistic effects. U.S. Patent No. 3,652,589 (the "Flick patent") teaches that acetaminophen can be combined with other analgesics including phenacetin, and instructs that such combinations are "proven to be of considerable therapeutic value." Example 23 of the Flick patent discloses a combination of phenacetin and acetaminophen in a ratio that falls squarely within that claimed in the RE221 patent. The only alleged difference between the tablet disclosed in the asserted claims of the RE221 patent and the tablet disclosed in example 23 is that the latter also contains two additional ingredients, pentobarbital sodium and ethoxy benzamide. Given that ethoxy benzamide was a known carcinogen and pentobarbital sodium was known to have antagonistic interactions with analgesics, it would have been obvious to remove these two drugs from Flick's formulation.

Indeed, Flick teaches that its four-agent tablet was merely an example of a possible combination tablet, stating that example 23 "illustrates the composition" of a combination tablet "without, however, limiting the same thereto." Flick also teaches that ingredients can be varied as desired. The patent states: "Of course, by variation and calculation of the ingredients tablets and other compositions are prepared containing lower or higher amounts of the essential active agents as desired." Nowhere does Flick state that pentobarbital sodium and ethoxy benzamide are required components in a tramadol/acetaminophen tablet. "If a person of ordinary skill can implement a predictable variation [of the prior art], § 103 likely bars its patentability." KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 417 (2007). Here, the removal of pentobarbital sodium and ethoxy benzamide was a predictable and simple variation on the Flick formulation. See id. at 421 ("A person of ordinary skill is . . . a person of ordinary creativity, not an automaton."); Bayer Schering Pharma AG v. Barr Labs., Inc., No. 2008-1282, 2009 U.S. App. LEXIS 17372 (Fed. Cir. Aug. 5, 2009) (affirming an obviousness determination where the patentee was confronted with a limited number of options for modifying a prior art pharmaceutical composition).

In addition to the Flick patent, several other prior art references (the "German references") explicitly teach that tramadol can be combined with acetaminophen to provide effective pain relief. Most of these references discuss combining tramadol and acetaminophen without any additional ingredients. Although the German references involve the administration of two separate tablets and adhere to an individualized, rather than fixed, dosing regimen, these differences are insufficient to preclude a finding of obviousness. When the German references are read in light of the combination fixed-

dose tablet disclosed in Flick, they clearly suggest combining tramadol and acetaminophen in a single fixed-dose tablet. Indeed, one of the German references laments the lack of available fixed-dose combination tablets, bemoaning the fact that "there are few fixed combinations of analgesics on the market."

Combining acetaminophen with tramadol was such an expected and logical step that one of Ortho's own research fellows, Fred Minn, M.D., Ph.D., testified that acetaminophen was the "obvious" drug to combine with tramadol and that he could not "think of anybody who didn't think of it." Minn further explained that it was a "natural phenomenon" for Ortho to combine tramadol with acetaminophen since Ortho had a long history "of combining [acetaminophen] with everything in the world."

The situation presented here parallels that presented in Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1480 (Fed. Cir. 1997). There we held that it would have been obvious to combine two drugs, the analgesic ibuprofen and the decongestant pseudoephedrine, in a single tablet since the drugs had been co-administered in the past. There, as here, it was manifestly obvious to combine two well-known drugs—which had previously been administered together—in a single tablet. See In re Diamond, 360 F.2d 214, 217-18 (C.C.P.A. 1966) (concluding that a combination of two therapeutic agents for inflammatory disease was obvious).

As the district court correctly concluded, the testimony of Ortho's expert, Donald Stanski, M.D., was insufficient to raise genuine issues of material fact on the obviousness question. Conclusory and unsupported expert testimony cannot serve as a bar to summary judgment. Although Stanski asserted that the prior art taught away from combining tramadol and acetaminophen in a fixed-dose composition, his testimony

is directly contradicted by the explicit teaching of Flick, which provides for a fixed dose tramadol/acetaminophen combination. Likewise, although Stanski argued that the alleged synergy of the claimed combination tablet was unexpected, Flick plainly states that "frequently a synergistic effect is observed" when combining tramadol with other analgesics such as phenacetin. Expert opinions must be given short shrift when they fly in the face of explicit disclosures in the prior art. See PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1361-62 (Fed. Cir. 2007) (refusing to credit an expert's testimony where it could not be "reconciled with statements made by the inventors in the joint specification and with . . . prior art references"); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 294 (Fed. Cir. 1985) ("Lack of factual support for expert opinion going to factual determinations, however, may render the testimony of little probative value in a validity determination.").

Indeed, when read as a whole, Stanski's testimony actually supports an obviousness determination. Ortho argues that one of ordinary skill in the art would not be motivated to remove the ingredients pentobarbital sodium and ethoxy benzamide that were listed along with tramadol and acetaminophen in example 23 of the Flick patent. Stanski, however, noted that "it is well established that barbiturates in low doses exhibit an antagonistic interaction with analgesics," and that by 1991, the priority date for the RE221 patent, a person of ordinary skill in the art would have appreciated that ethoxy benzamide had "carcinogenic properties." Stanski's testimony, therefore, supports the conclusion that a skilled artisan would have been motivated to remove pentobarbital sodium and ethoxy benzamide from Flick's tramadol/acetaminophen tablet.

Simply put, there is nothing even arguably new about what Ortho claims to have invented. I would affirm.