United States Court of Appeals for the Federal Circuit

TYCO HEALTHCARE GROUP LP
AND MALLINCKRODT, INC.,
Plaintiffs-Appellants,

v.

MUTUAL PHARMACEUTICAL COMPANY, INC.
AND UNITED RESEARCH LABORATORIES, INC.,
Defendants-Appellees.

2010-1513

Appeal from the United States District Court for the District of New Jersey in Case No. 07-CV-1299, Judge Stanley R. Chesler.

Decided: June 22, 2011

HENRY J. RENK, Fitzpatrick, Cella, Harper & Scinto, of New York, New York, argued for the plaintiffs-appellants.

JEREMY C. LOWE, Axinn, Veltrop & Harkrider LLP, of Hartford, Connecticut, argued for defendants-appellees. With him on the brief were JAMES D. VELTROP and

FRANCIS H. MORRISON, III,. Of counsel were THOMAS K. HEDEMANN and JASON T. MURATA.

Before NEWMAN, BRYSON, and GAJARSA, *Circuit Judges*.

BRYSON, *Circuit Judge*.

Tyco Healthcare Group LP and Mallinckrodt, Inc. (collectively, "Tyco") appeal from a summary judgment invalidating the two claims of U.S. Patent No. 5,211,954 ("the '954 patent") for obviousness. We affirm.

I

Temazepam is a hypnotic (sleep-inducing) drug that is one of a class of compounds known as benzodiazepines. Pharmacological formulations of temazepam have been marketed internationally for the treatment of insomnia since the 1970s, and in the United States since 1981 under the name Restoril®. Tyco holds the rights to the '954 patent, which has two claims for temazepam formulations. Claim 1 reads:

> A hard gelatin capsule containing a temazepam formulation consisting essentially of 6 to 8 milligrams of crystalline temazepam having a surface area of from 0.65 to 1.1 m^2/g and 95% of the temazepam having a particle size of less than 65 microns in admixture with a pharmaceutically acceptable carrier therefor.

Claim 2 is identical except that it recites a composition containing 7.5 milligrams of crystalline temazepam. The '954 patent issued in May 1993 with a priority date of September 1986. Tyco's predecessor-in-interest began marketing Restoril® in 7.5 mg dosages in 1991.

In November 2006, Mutual Pharmaceutical Company, Inc., filed an Abbreviated New Drug Application ("ANDA") with the U.S. Food and Drug Administration ("FDA") seeking approval to manufacture and sell a generic version of 7.5 mg temazepam capsules. Tyco responded in March 2007 by filing an infringement action against Mutual and United Research Laboratories, Inc. (collectively, "Mutual"). In July 2009, after Mutual had received tentative FDA approval of its ANDA, Tyco moved for a preliminarily injunction to prevent Mutual from selling its generic temazepam capsule. The district court denied Tyco's motion based on uncontroverted evidence that Mutual's ANDA disclosed a product that could not literally infringe the '954 patent because the ANDA required the surface area of the crystalline temazepam to be at least 2.2 square meters per gram. *See Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1249 (Fed. Cir. 2000).

Mutual then moved for summary judgment of non-infringement and invalidity. The district court granted Mutual's motion with respect to invalidity, concluding that Mutual had shown by clear and convincing evidence that the '954 claims were obvious and that no reasonable trier of fact could find to the contrary. In reaching that conclusion, the court noted, first, that Restoril® capsules had been sold in the United States in 15 mg and 30 mg dosages more than a year before the priority date of the '954 patent. Second, the court looked to a 1983 volume of the British National Formulary ("BNF"), a medical reference book published in the United Kingdom, which directed physicians to the use of temazepam at a dosage between 5 and 15 mg for the treatment of insomnia in the elderly. Third, the court observed that the parties did not dispute that "physicians always seek to prescribe the lowest effective dose of any medication, particularly

hypnotics such as temazepam." Based on those undisputed facts, the court concluded that it would have been obvious to a person of ordinary skill in the art to combine the preexisting 15 mg Restoril® capsule with the dosage range identified in the BNF reference. Tyco appeals the district court's order invalidating the '954 claims.

II

The only physical feature distinguishing the '954 claims from the Restoril® 15 mg capsules is the amount of temazepam contained in the capsule. In 1987, Tyco's predecessor-in-interest filed a Supplemental New Drug Application with the FDA for manufacture and sale of 7.5 mg temazepam capsules within the scope of both '954 claims. The application stated that:

> [t]he formulation and manufacture of Restoril® Capsules, 7.5 mg are similar to that used for the 15 and 30 milligram capsules . . . . The formulation differs only in the reduction of the dose. . . . The capsule manufacturing method is exactly the same as has been described for the currently marketed doses.

Given that uncontested description, the only limitation of the two '954 claims that was not fully disclosed by the prior art Restoril® capsules is the lower dosage of temazepam.

The BNF is a medical reference book published semiannually by the British Medical Association and the Pharmaceutical Society of Great Britain. The Preface to the BNF explains that it serves as "a pocket book for rapid reference . . . for prescribing and dispensing" drugs, and that its entries "are intended to help in the choice of

appropriate treatment of each patient." The 1983 BNF entry for "temazepam" reads as follows:

> ***Indications:*** insomnia (useful in the elderly)
>
> ***Cautions; Side-effects:*** see under Nitrazepam,[1] but except at high dosage hangover is uncommon and doses less cumulative. Less appropriate in patients with early wakening
>
> ***Dose:*** 10-30 mg (*elderly patients 5-15 mg*), increasing in severe insomnia to 60 mg, 30 minutes before bedtime

BNF at 127 (emphasis added). The district court concluded that "[t]his entry plainly tells one of skill in the art to treat insomnia in the elderly by administering a dose in the range of 5 to 15 mg."[2] The court noted that a physi-

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[1] The BNF entry for "nitrazepam" reads, in relevant part:

> ***Cautions:*** hangover may affect a patient's ability to drive or operate machinery and increase the effects of alcohol; avoid prolonged use and abrupt withdrawal thereafter. Caution in neuromuscular disease, respiratory disease, pregnancy, breast-feeding, patients with a history of drug abuse; *reduce dosage in elderly and debilitated patients* . . . .
>
> ***Side-effects:*** hangover with drowsiness, dizziness, ataxia (*particularly in the elderly*); occasionally confusion, dry mouth, hypersensitivity reactions. Prolonged use may give rise to cumulation, tolerance, rebound insomnia, and dependence.

BNF at 127 (emphases added).

[2] The district court's interpretation of the BNF reference is consistent with evidence in the record of a statement made in 1984 by an FDA representative to a group that included the named inventor of the '954 pat-

cian would be motivated to prescribe a temazepam dosage lower than 15 mg because of the preference for the lowest effective dose, particularly in the case of elderly patients sensitive to the side effects of hypnotic medications.

Ordinarily, "where there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004); *accord Lazare Kaplan Int'l, Inc. v. Photoscribe Techs., Inc.*, 628 F.3d 1359, 1380-81 (Fed. Cir. 2010). That presumption is rebuttable either by a showing that the prior art taught away from the invention or by a showing of new and unexpected results relative to the prior art. *Iron Grip Barbell*, 392 F.3d at 1322. Tyco argues first that the BNF reference does not direct a person of ordinary skill in the art to temazepam hard capsules in the 5 to 15 mg dosage range. It then argues that the prior art as a whole taught away from a range of 6 to 8 mg. Finally, Tyco contends that secondary considerations of new and unexpected results and commercial success support a finding of non-obviousness.

A

Tyco contests the district court's interpretation of the BNF reference. It relies on the declaration of its expert, Dr. William Orr, who stated that "[a] person of ordinary skill in the art would not interpret [the BNF] reference as

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ent. According to notes of a meeting to discuss a "proposed course of action to further characterize the profile of [Restoril]," Dr. Hillary Lee of the FDA stated that "the doses proposed in [the] studies may be too high, citing that in Great Britain, temazepam doses from 5-15 mg are recommended for geriatrics and doses from 15-30 mg for adults."

recommending any particular dose." The district court, however, concluded that Dr. Orr had not offered a factual basis for his conclusion or explained his rationale and therefore discredited his characterization of the BNF.

In support of his interpretation of the BNF reference, Dr. Orr stated that the BNF reference "nowhere states that a temazepam dose of 5 mg, 6 to 8 mg, or 7.5 mg, is effective in treating insomnia," nor does it "state that 7.5 mg was effective." He added that the BNF reference provides "[n]o clinical or statistical evidence . . . demonstrating that a dose within a range of 5-15 mg would work" in treating insomnia.

Those statements by Dr. Orr correctly describe the contents of the BNF reference, but they do not undermine the district court's conclusions as to obviousness. The '954 claims do not discuss the intended use of the capsules in a particular treatment regimen. The manufacture of a 7.5 mg temazepam capsule with the disclosed claim limitations would infringe both claims of the '954 patent, irrespective of the efficacy of the product. Dr. Orr's statements did not contest the fact that the BNF refers to dosages of temazepam between 5 and 15 mg.[3] His state-

[3] At oral argument, Tyco's counsel argued that Dr. Orr's declaration should be interpreted to mean that the reference to "5-15 mg" did not disclose all dosages between 5 and 15 mg. Counsel argued that the BNF reference, "while it has 5 dash 15, a person of ordinary skill in the art would know that it cannot refer to 7.5 specifically. It refers to 5 arguably, perhaps a 10, perhaps a 15 . . . ." That argument is silly. Not only is it contrary to the ordinary understanding that a dash joining two numbers signifies the end points of an inclusive range, but it also is at odds with Dr. Orr's own reference to "5-15 mg" as constituting a "range."

ments are directed to the utility of temazepam as a treatment for insomnia.

Tyco argues that all the properties of a composition of matter relevant to patentability must be considered in evaluating whether that composition would have been obvious in light of the prior art, and that the unclaimed property of effectiveness in treating insomnia renders the claims at issue nonobvious. That argument is unavailing. "The discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, can not impart patentability to the known composition." *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990) (noting that "a new use of a known composition . . . may be patentable as a process"). The recommendation in the BNF of a range of temazepam dosages that include the dosages claimed in the '954 patent renders obvious the claims to those dosages even in the absence of documentation in the BNF of the effectiveness of such dosages.

Dr. Orr noted that the BNF reference listed several brands of commercially available temazepam formulations, which had dosages of 10 mg and 20 mg, but not 5 mg. That observation, however, does not call into doubt what the BNF reference disclosed. Tyco does not dispute that, at the time the BNF was published, 5 mg temazepam hard capsules had been sold abroad for more than a decade under the name Levanxol®. In addition, the record contains two prior art publications discussing experimentation with 5 mg capsules: a 1970 Italian study ("Senini") and a 1974 Indian study ("Sardesai").

Finally, Dr. Orr stated that one of skill in the art, reading the Preface to the BNF reference, "would understand that one must look to other, 'specialised publica-

tions'—*i.e.*, scientific publications relating to the effectiveness of temazepam doses—in order to determine whether any particular dose is effective." Again, Dr. Orr's position does not undermine the BNF as a supporting reference. First, as already discussed, the '954 claims are not tied to product efficacy, so the absence of any particularized discussion of efficacy in the BNF reference is immaterial to obviousness of the composition here claimed in light of the prior art showing general efficacy for the same use. Second, none of the specialized publications cited by Dr. Orr and Tyco undermine the teaching of the BNF reference that a person of ordinary skill in the art could consider temazepam dosages between 5 mg and 15 mg to treat insomnia.

B

Two of the specialized publications cited by Tyco are articles from the 1970s by the same authors ("Nicholson 1976" and "Nicholson 1979"). The first reference, Nicholson 1976, described a sleep study conducted with six males between the ages of 19 and 43. The experimenters administered 10 mg and 20 mg doses of temazepam to the subjects. The experiment disclosed that 10 mg temazepam doses produced a "marked reduction in sleep onset latency"—i.e., the time it takes a person to fall asleep—but resulted in "little or no increase in total sleep time."

Tyco argues that Nicholson 1976 taught that 10 mg capsules were "ineffective because they do not affect the 'key' requirement of total sleep time." According to Tyco, "effectiveness as a sleeping pill requires both that sleep latency is decreased and total sleep time is increased." Tyco cites the '954 patent, Dr. Orr's declaration, and a 1983 publication ("Matejcek") in support of that proposition. The '954 patent discusses experimental findings

that 7.5 mg temazepam capsules reduced sleep onset latency and increased total sleep time. '954 patent, col. 2, ll. 32-34. Dr. Orr declared that "[t]he only means to conclusively verify a hypnotic agent's effect on sleep patterns is to conduct studies specifically designed to record additional polysomnographic parameters such as total sleep time and sleep latency" because only such studies "give reliable indications of whether any particular treatment is effective." Matejcek, discussed further below, stated that "effects on the sequence, duration, and relative depth of individual sleep stages . . . have been used to estimate latency to sleep onset and the relative potency and duration of drug activity." Although each of those sources refers to both sleep onset latency and total sleep time, none states that a sleeping pill must achieve improvement on both parameters in order to be considered effective. Therefore, the evidence in the record does not support Tyco's contention that Nicholson 1976 taught away from 10 mg temazepam doses.

Tyco also points out that Nicholson 1976 taught that 20 mg temazepam capsules are effective for treatment of insomnia. The study found a statistically significant increase in total sleep time and decrease in sleep onset latency following administration of 20 mg temazepam capsules. However, that result is not pertinent to the issue in this case because it does not teach away from the efficacy of 7.5 mg capsules.

The second reference, Nicholson 1979, described a sleep study conducted with six middle-aged males between the ages of 45 and 55. The experimenters administered 10, 20, and 30 mg doses of temazepam. The experimental results revealed no statistically significant change in total sleep time or sleep onset latency after administration of any of those dosages of temazepam. All

three dosages, however, resulted in statistically significant reductions in the duration of awakenings during the night.

Tyco contends that "the temazepam soft capsules produced in the older group a 'marked reduction' in total sleep time and an 'increase' in latency to certain sleep stages, exactly the opposite of what one wants in a sleep aid." The portion of Nicholson 1979 from which those quotations were drawn, however, discusses a comparison of general sleep patterns between young adults (ages 20 to 29) and middle-aged adults, using a placebo treatment for both groups. Apart from that mischaracterization of the Nicholson 1979 reference, the only point that Tyco makes about that study is that no dosage of temazepam—10, 20, or 30 mg—yielded a statistically significant improvement in total sleep time or sleep onset latency.

Tyco also relies on Matejcek, which described a daytime experiment administering various dosages of temazepam to 12 males between the ages of 20 and 30. That study, like those disclosed in the Sendai and Sardesai references, included the use of 5 mg capsules of temazepam. Tyco seizes on a remark in the "Results" section of the article in which the authors stated that "temazepam 5-mg values were excluded from the test procedure [measuring a particular type of brain wave activity], since this dose is known to be of no clinical importance as a hypnotic." Contrary to that statement, Matejcek did include 5 mg temazepam capsules in its test procedure and displayed results for those capsules in two tables in the article. Those tables revealed a statistically insignificant decrease in "alpha-activity" for 5 mg dosages of temazepam and statistically significant decreases for 15 mg and 30 mg dosages.

Tyco argues that "Matejcek would have directly discouraged [a person of ordinary skill in the art] from the idea that hard capsules with 7.5 mg of temazepam would be effective to treat insomnia." That argument is predicated on the position taken by Tyco in this court that the effectiveness of particular doses of temazepam depends on whether the capsule is hard or soft. According to Tyco, each milligram of temazepam delivered in soft capsule form is equivalent to 1.5 mg delivered in hard capsule form. Therefore, Tyco asserts, the fact that the 5 mg temazepam capsule had statistically insignificant effects on certain brain wave activity would have cast doubt on the efficacy of the claimed 7.5 mg capsules.

There are two problems with Tyco's argument. First, the Matejcek study did not identify whether hard or soft capsules were used in its experiment. The prosecuting attorney for the '954 patent represented to the PTO that Matejcek "clearly state[s]" that the capsules used were soft capsules, but there is no support for that statement in the record. After Mutual pointed out the lack of evidence on that point in its brief, Tyco refrained from characterizing the Matejcek capsule as a soft capsule in its reply brief.

Second, the only prior art reference in the record before this court that could conceivably have given rise to Tyco's alleged 1:1.5 efficacy ratio is a published article from 1977 ("Fuccella 1977"). That reference disclosed an experiment on six males between the ages of 21 and 33 using both soft and hard capsules of temazepam, and the last paragraph of the article states:

> It is interesting that in a study of its effect on sleep, temazepam 20 mg in Scherer capsules was significantly better than 30 mg of the same sub-

> stance in hard conventional capsules according to a subjective evaluation of quality of sleep, awakening from sleep and impairment of behaviour [reference]. The results of these studies are in keeping with bioavailability from soft gelatin capsules and the pharmacokinetic profile of temazepam.

Essentially, Tyco's argument is based on a passing mention in an article of a subjective sleep evaluation study described in another article in which 20 mg soft capsules performed better than 30 mg hard capsules. However, Tyco did not refer to either of those articles as relevant prior art in its opening brief. Moreover, according to Tyco's own argument that measurement of several objective sleep parameters (e.g., sleep onset latency and total sleep time) is required to evaluate the efficacy of a sleeping pill, the subjective sleep evaluation study that could ultimately have led to Tyco's 1:1.5 ratio would not have been able to measure sleeping pill efficacy with accuracy. Nor did the Matejcek study measure those parameters. In sum, Tyco's argument that the Matejcek reference teaches away from use of a 7.5 mg hard capsule of temazepam to treat insomnia is not supported by evidence in the record.

Furthermore, none of the relevant references cited by Tyco[4]—Nicholson 1977, Nicholson 1979, and Matejcek—

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[4] Tyco argues that "as late as 1989 the FDA recommended a 'usual' hard capsule adult dose of 30 mg . . . [and] counseled that a hard capsule dose of 15 mg 'may be sufficient in some patients.'" In support, it cites to a page of the 1989 edition of the Physicians' Desk Reference, a medical reference book published commercially. The passages quoted by Tyco do not suggest that dosages less than 15 mg would be insufficient in all patients. In fact,

studied the effects of temazepam on elderly patients. The BNF reference specifically directed readers to a lower dosage of temazepam for the elderly, given the increased risk of side effects such as ataxia. Even if the references cited by Tyco could be viewed as teaching away from the use of 7.5 mg temazepam capsules generally, it would not cast doubt on the BNF reference's dosage range for elderly patients. To the contrary, Nicholson 1979 cited other studies "suggest[ing] that hypnotics may have an enhanced effect in old age," including "increased sensitivity" and an increased "effect on performance." If anything, such statements, viewed in light of the undisputed preference of physicians for prescribing the lowest effective dosage of temazepam, point toward the use of lower-dosage capsules.

C

Tyco argues that secondary considerations support a finding of non-obviousness of the '954 claims. It contends that the experimental results described in the '954 patent were unexpected. In support, Tyco cites the patent specification's description of the inventor's experimental results as "unexpected." '954 patent, col.2, ll.34-36. Unsupported statements in the specification, however, cannot support a finding of unexpected results. *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984).

Tyco also contends that "experts expressed skepticism about . . . possible effectiveness at the time the invention was made." It first cites a memorandum prepared by the original assignee of the '954 patent memorializing a 1984

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the reference notes that "the risk of development of oversedation, dizziness, confusion and/or ataxia increases, substantially with larger doses of benzodiazepines in elderly and debilitated patients . . . ."

meeting. That document relates the opinion of a "sleep expert consultant" that transient insomniacs might require a higher dosage of temazepam for treatment than chronic insomniacs. Since the products disclosed by the claims at issue are not limited to treatment for transient insomnia, that statement is of little relevance to the question whether 7.5 mg capsules were unexpectedly effective. In any event, the district court did not find evidence in the memorandum casting doubt on the efficacy of 7.5 mg capsules.

Tyco next points to a 1985 letter sent by an FDA expert to the company employing the named inventor asking the company to "provide the rationale for the choice of the 7.5 mg dosage" in its experiment. The motivation for that request was not disclosed in the letter. That letter provides no indication that the FDA expert would have been surprised at the results disclosed in the '954 patent.

Tyco also cites Dr. Orr's declaration that, in light of the prior art already discussed, the results of the inventor's experiment would have been surprising at the time. That statement is entitled to little weight in light of the lack of support in the record for Dr. Orr's interpretation of the prior art. Tyco does not supply further evidence of unexpected results other than citations to the prior art previously discussed. On the evidence and argument in the summary judgment record, Tyco has not overcome Mutual's clear and convincing showing of obviousness.

Finally, Tyco argues that the commercial success of Restoril® 7.5 mg capsules supports a finding of nonobviousness. It notes that over the past decade, annual sales of the capsules have averaged more than $30 million. The district court acknowledged the product's commercial success but properly found that the evidence as a whole did not overcome Mutual's strong prima facie case

of obviousness. *See Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 719 (Fed. Cir. 1991); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 413 (2007) (upholding district court's summary judgment of invalidity for obviousness despite evidence of commercial success); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 61 (1969). We therefore uphold the summary judgment determination of the district court that the two claims of the '954 patent are invalid for obviousness. In light of our decision, Mutual's motion to strike portions of Tyco's reply brief is denied as moot.

AFFIRMED