United States Court of Appeals for the Federal Circuit

03-1168

MERCK & CO., INC.,

Plaintiff-Appellee,

v.

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellant,

and

ZENITH GOLDLINE PHARMACEUTICALS, INC.,

Defendant-Appellant.

John F. Lynch, Howrey Simon Arnold & White, LLP, of Houston, Texas, argued for plaintiff-appellee. With him on the brief were Nicolas G. Barzoukas, Richard L. Stanley, and Scott J. Garber. Of counsel on the brief were Paul D. Matukaitis, Edward W. Murray, and Gerard M. Devlin, Merck & Co., Inc., of Rahway, New Jersey.

James Galbraith, Kenyon & Kenyon, of New York, New York, argued for defendant-appellant Teva Pharmaceuticals USA, Inc. With him on the brief were Maria Luisa Palmese and William G. James, II. William L. Mentlik, Lerner, David, Littenberg, Krumholz & Mentlik, LLP, of Westfield, New Jersey, argued for defendant-appellant Zenith Goldline Pharmaceuticals, Inc. With him on the brief was Stephen F. Roth.

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

Judge Joseph J. Farnan, Jr.

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DECIDED: October 30, 2003

Before MAYER, Chief Judge, NEWMAN and PROST, Circuit Judges.

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

NEWMAN, Circuit Judge.

Teva Pharmaceuticals USA, Inc., and Zenith Goldline Pharmaceuticals, Inc., (collectively "Teva") appeal the judgment of the United States District Court for the District of Delaware, ruling that Teva infringes United States Patent No. 4,621,077 ("the '077 patent") owned by Merck & Co., and that the patent is not invalid.[1] We affirm the judgment.

Standard of Review

We review a district court's judgment, following a bench trial, to determine whether there were errors of law or clearly erroneous findings of fact. Allen Eng'g Corp. v. Bartell Indus., Inc., 299 F.3d 1336, 1343-44 (Fed. Cir. 2002); Manville Sales Corp. v. Paramount Sys. Inc., 917 F.2d 544, 549 (Fed.

Cir. 1990).

In determination of patent infringement, as the first step the claims are construed; then, the construed claims are compared to the alleged infringing device. Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1323 (Fed. Cir. 2002). Claim construction is a matter of law, and receives plenary review on appeal. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc). Anticipation is a question of fact, and after a bench trial is reviewed under the clearly erroneous standard. Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1458 (Fed. Cir. 1984). A factual finding is clearly erroneous when "although there is evidence to support it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." United States v. U.S. Gypsum Co., 333 U.S. 364, 395 (1948).

DISCUSSION

Merck acquired the '077 patent from its original owner Istituto Gentili, S.p.A. The patent issued on November 4, 1986. Its term has been extended for 1,371 days, measured as a portion of the time consumed by regulatory review and approval by the Food and Drug Administration. See 35 U.S.C. §156. The sole claim of the '077 patent is:

> 1. A method of treatment of urolithiasis and inhibiting bone reabsorption which consists of administering to a patient in need thereof an effective amount of 4-amino-1-hydroxybutane-1,1-biphosphonic acid.

The product has been given the common name alendronic acid.

Merck's product, marketed under the brand name Fosamax®, is 4-amino-1-hydroxybutane-1,1-biphosphonic acid monosodium salt trihydrate, also called alendronate salt. In September of 1995 Merck received Food and Drug Administration approval to market Fosamax® for treatment of osteoporosis and Paget's disease. Teva, a generic drug manufacturer, filed an abbreviated new drug application (ANDA) to sell a generic version of Fosamax®. Merck duly sued Teva in accordance with 35 U.S.C. §271(e)(2). Teva's defense was that the '077 patent is invalid or not infringed, and alternatively that Merck is not entitled to any extension of the patent term because the approved product is not the acid but the monosodium salt. Teva stated that it did not literally infringe because the claim

requires 4-amino-1-hydroxybutane-1,1-biphosphonic acid and Teva's ANDA is for the monosodium salt. Teva also raised the defense that United States Patent No. 4,407,761 to Helmut Blum et al. anticipates the claim.

I

INFRINGEMENT

The district court ruled that the claim is infringed by Teva's product. The court found that the claimed method whereby 4-amino-1-hydroxybutane-1,1-biphosphonic acid is used to treat urolithiasis and bone reabsorption disorders (such as osteoporosis) is infringed by administration of the acid salt. The therapeutic agent of the claim is 4-amino-1-hydroxybutane-1,1-biphosphonic acid, whose application is exemplified in the specification in formulations that include the salt and admixtures of the biphosphonic acid with a salt-forming material. The patent refers to formulation of various biphosphonic acids for administration "as the sodium salt," "in the salt form," "in the form of Na salt," and as "4-amino-1-hydroxybutan-1,1-biphosphonic acid, sodium salt."

Specification Table 6 is headed: "Some typical pharmaceutical formulations containing amino-butan-diphosphonic acid," and shows the diphosphonic acid formulated in three ways: (1) as "opercolated capsules" containing "4-amino-1-hydroxybutan-1,1-biphosphonic acid, sodium salt"; (2) as "effervescent granulates" where the formulation includes 4-amino-1-hydroxybutan-1,1-biphosphonic acid, sodium carbonate, and sodium bicarbonate; and (3) "formulations suitable for injection" where the ingredients include 4-amino-1-hydroxybutan-1,1-biphosphonic acid and sodium hydroxide. The witnesses qualified in the field of the invention testified that a pharmacologist of ordinary skill in the field would understand that the active agent is 4-amino-1-hydroxybutane-1,1-biphosphonic acid, and that the method of treatment of bone disorders includes use of the active agent in the form of the salt.

This usage is clearly presented in the specification. In addition to the formulations in Table 6, patent Tables 7 and 8 compare the potency of various biphosphonates that are listed as the acids "in the form of" the salt, and the specification describes various biphosphonic acids "in the form of" the salt; e.g.:

difluoromethanebiphosphonic acid in the form of the Na salt
dichloromethanebiphosphonic acid in the form of the sodium salt

'077 patent, col. 9, lines 26-51. The specification describes the unusually high activity of 4-amino-1-hydroxybutane-1,1-biphosphonic acid in an in vivo rat model for inhibition of bone resorption, exemplified in application as the salt. The footer in Table 7 refers to the compounds as "various aminobiphosphates" and includes the compound "AHBuBP," which is defined as the biphosphonic acid here at issue, although the "phosphate" terminology generally refers to salts. Thus throughout the specification the inventors described the acid active agent as encompassing the acid and its salt forms.

In evidence were several technical publications that describe treatment with biphosphonic acids in terms that include treatment using the salt form. In an article entitled "Alendronate: A New Biphosphonate for the Treatment of Osteoporosis," the caption names the product "4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid" and Figure 1 depicts the sodium salt. In an article entitled "Rationale for the Use of Alendronate in Osteoporosis," a diagram of the structure of the sodium salt is labeled both as "Alendronate" and as "4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid." An article entitled "Advances in the Management of Paget's Disease of Bone" refers to three different diphosphonates by their common names, using a description encompassing the acid and salt forms: "eudronic acid (disodium eudronate)," "clodronic acid (clodronate)," and "pamidronic acid (pamidronate)." These are the same usages employed in the '077 specification.

In construing patent claims, the court must apply the same understanding as that of persons knowledgeable in the field of the invention. "Patents are written not for laymen, but for and by persons experienced in the field of the invention." Voice Techs. Group, Inc. v. VMC Sys., Inc., 164 F.3d 605, 615 (Fed. Cir. 1999). See Hoechst Celanese Corp. v. B.P. Chems. Ltd., 78 F.3d 1575, 1578 (Fed. Cir. 1996) ("A technical term used in a patent document is interpreted as having the meaning that it would be given by persons experienced in the field of the invention, unless it is apparent from the patent and the prosecution history that the inventor used the term with a different meaning.").

The district court found that a person skilled in the treatment of osteoporosis and urolithiasis would have a medical degree, knowledge of the methods of treatment of patients with these disorders, and knowledge of the pharmacology and usage of biphosphonates. The court determined how such

persons would understand the claim in light of the specification, its prosecution history, and customary usage in the field of the invention. See Toro Co. v. White Consol. Indus., Inc., 199 F.3d 1295, 1299 (Fed. Cir. 1999).

A fundamental rule of claim construction is that terms in a patent document are construed with the meaning with which they are presented in the patent document. Bell Atl. Network Servs., Inc. v. Covad Communications Group, Inc., 262 F.3d 1258, 1267-68 (Fed. Cir. 2001); Multiform Desiccants, Inc. v. Medzam, Ltd., 133 F.3d 1473, 1477 (Fed. Cir. 1998). Thus claims must be construed so as to be consistent with the specification, of which they are a part. Gen. Am. Transp. Corp. v. Cryo-Trans, Inc., 93 F.3d 766, 770 (Fed. Cir. 1996); Slimfold Mfg. Co. v. Kinkead Indus. Inc., 810 F.2d 1113, 1117 (Fed. Cir. 1987).

The claim herein is directed to a method of treatment of urolithiasis and inhibiting bone reabsorption, by administering an effective amount of the specified biphosphonic acid. The evidence of all the qualified witnesses was that persons in this field would understand that the acid is the active agent and that the acid is administered when it is in the form of the salt. There was no evidence that the claimed method of treatment is not achieved by the acid salt. The record shows that Teva and Zenith, as well as Merck, label their products with the "free acid equivalent."

The record contains extensive evidence that persons experienced in this field use the same lexicography as did the inventors in referring to the active ingredient "in the form of" the salt. See Multiform Desiccants, 133 F.3d at 1477 (the inventor's words "must be understood and interpreted by the court as they would be understood and interpreted by a person in that field of technology"). Dr. Recker, an expert on behalf of Merck, testified that the '077 patent uses the word "acid" to encompass the sodium salt, and that to a pharmacologist this usage is well understood. The cited articles match this usage. The Director of the Patent and Trademark Office also so recognized, in informing the Food and Drug Administration that the patent covers the federally registered product.

The only contrary evidence was provided by a Teva witness who was a chemist and who conceded that he was not qualified in pharmacology. He testified that an acid is not a salt. The district court discounted this testimony, recognizing the absence of qualification of the witness in the field of the

invention. The specification shows that the inventors knew the chemical difference between an acid and a salt, for they described the pharmacologic use of the acid "as the salt," and referred to the "biphosphonic acid, sodium salt." The district court placed weight on the evidence of persons qualified in the field of the invention, as against the simplified answer of a witness who, although qualified as a chemist, was notable for his distance from the field of pharmacology.

The question is not whether a general chemist would know the difference between an acid and a salt. The question is whether a person experienced in the field of the invention and familiar with the usages of pharmacology and the prior art, reading the patent specification, would know that for the treatment of urolithiasis and to inhibit bone reabsorption, the statement that 4-amino-1-hydroxybutane-1,1-biphosphonic acid is administered to treat these diseases, encompasses administration as the acid salt. All of the pharmacologist witnesses agreed that this was the correct reading.

Teva argues that it is improper to go outside of the prosecution record to explain the meaning of terms used in a patent claim. It is well established that evidence extrinsic to the patent documents cannot change the meaning of a term as used in the claim from the meaning with which it is used in the specification. However, it is not prohibited to provide the opinions and advice of experts to explain the meaning of terms as they are used in patents and as they would be perceived and understood in the field of an invention. See Omega Eng'g, Inc. v. Raytek Corp., 334 F.3d 1314 (Fed. Cir. 2003); Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1309, (Fed. Cir. 1999). We conclude that there was not reversible error in the court's crediting of the pharmacologists' testimony, buttressed by publications, the usages in the specification, and the view of the PTO, as against the testimony of a chemist without experience in the specific field of the invention.

The prosecution history is not contrary to this conclusion, for the cancellation of the composition claims was not a disclaimer of the specific method described in the '077 patent. The method claim was entered and allowed upon the examiner's rejection of the composition claims. The new use of a known composition is claimed as a method. See 35 U.S.C. §100(b) (Eligible methods include "a new use of a known process, machine, manufacture, composition of matter, or material."); Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 875 (Fed. Cir. 1985). The specification shows that the active ingredient in the claimed method is the biphosphonic acid; there was no rejection of the method claim during

prosecution, and no departure from the meaning of the terms as used in the specification.

We affirm the district court's holding that the claimed method of treatment by administration of the biphosphonic acid is infringed whether administered as the pure acid or in the form of the acid salt.

II

VALIDITY

Teva also argues that United States Patent No. 4,407,761 ("Blum") anticipates the '077 patent. Blum describes various biphosphonic acids including 4-amino-1-hydroxybutane-1,1-biphosphonic acid, and states that they are useful as sequestering agents for polyvalent metals and as water softeners, and are "suitable for the production of cosmetic and pharmaceutical preparations." Blum, col. 3, lines 30-40. Teva argues that because Blum mentioned "pharmaceutical preparations," one of ordinary skill in the art would know that the compounds are useful for therapeutic treatments such as in claim 1 of the '077 patent. However, there is no suggestion of the claimed therapeutic uses in Blum; and Blum does not identify the particular compound of the claim as having superior bone reabsorption properties. An "anticipating" reference must describe all of the elements and limitations of the claim in a single reference, and enable one of skill in the field of the invention to make and use the claimed invention. Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1378-79 (Fed. Cir. 2001); Richardson v. Suzuki Motor Co., 868 F.2d 1226 (Fed. Cir. 1989). Such description is absent in Blum. Reversible error has not been shown in the district court's ruling that the claim is valid.

III

PATENT TERM RESTORATION

Teva argues that the extension of the '077 patent term, as approved by the Patent and Trademark Office and the Food and Drug Administration, is invalid because the patent claim is directed to the acid, while the FDA-approved product is the acid salt. The district court held that the patent is entitled to term extension. We take note that Fosamax® was not approved for sale until after nine years of patent life had elapsed.

The relevant statute, 35 U.S.C. §156, provides for extension of the patent term for a portion of the time consumed by federal regulatory approval:

> §156. Extension of Patent Term
>
> > (a) The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section . . . , if --
> >
> > * * *
> >
> > (4) the product has been subject to a regulatory review period before its commercial marketing or use . . . .

35 U.S.C. §156(f) defines "product" as including "any salt or ester of the active ingredient":

> §156(f). For purposes of this section:
>
> (1) The term "product" means
>
> (A) A drug product.
>
> * * *
>
> (2) The term "drug product" means the active ingredient of--
> (A) A new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act), . . .
>
> * * *
>
> including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.

The FDA regulations define "active ingredient" as "any component that is intended to furnish pharmacological activity . . . or to affect the structure or any function of the body." 21 C.F.R. §60.3(b)(2). The Hatch-Waxman Act, codified at 21 U.S.C. §355 and 35 U.S.C. §156(f), states that "active ingredient" includes a salt or ester of the active ingredient. These statutes and regulations implement the legislative purpose, by providing that the frequent use of salts or esters in a non-therapeutic part of the molecule does not defeat the purposes of the Act. The fact that the active moiety is administered as the acid salt is contemplated in the governing law.

In administering these provisions, appropriate deference is given to the expertise of the agency

charged with this authority and responsibility. See Dickinson v. Zurko, 527 U.S. 150, 152 (1999) (principles of administrative deference apply to PTO actions); Martin v. Occupational Safety & Health Review Comm'n, 499 U.S. 144, 151 (1991) (adjudications that are delegated by statute to the agency warrant judicial deference). The Director of the Patent and Trademark Office is charged with the decision of whether the patent is entitled to term extension. 35 U.S.C. §156(d). The Director determined that the '077 patent "does claim the active ingredient of the proposed product," and duly so notified the Secretary. Id. See Glaxo Operations UK Ltd. v. Quigg, 894 F.2d 392, 399 (Fed. Cir. 1990) ("we will give great deference to the Commissioner's determinations as to which patented chemical compounds fall within Congress' definition of 'products,' but little or no deference to the Commissioner's surmise of Congress' intent in framing its definition"). We agree with the Director's determination, and with its implementation by the Food and Drug Administration.

We therefore affirm the district court's conclusion that Merck is entitled to the allotted term extension.

AFFIRMED

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MAYER, Chief Judge, dissenting.

I agree with the court to the extent that it upholds the validity of '077 patent; however, because I believe that the district court erred in its claim construction by concluding that the term "acid" as used in the claim should be construed to encompass both acids and salts, I dissent. Such construction does not accord with a plain reading of the claim or the claim in light of the specification.

In a few instances in the specification of the '077 patent, alendronic acid is named when actually referring to the salt. But in the vast majority of instances, the specification distinguishes between the two. For example: the specification lists as the preferred embodiments, inter alia, 4-amino-1-hydroxybutane-1,1-biphosphonic acid and its sodium, aniline, and lysine salts, '077 patent, col. 3, ll. 20-26; in the "Toxicology Study" section of the specification, tests were conducted for the acid and the salt,

listing them as separate compounds, id. at col. 6, ll. 48-49; and in a discussion of the bone reabsorption and in vivo calcification experiments, the acid is juxtaposed with the name of another compound that is characterized as the sodium salt, id. at col. 9, ll. 45-51. These examples, and there are others, evidence that the acid and the salt are distinct compounds and that the patentee is able to distinguish between the two when he so chooses.

Further support for the proposition that the two are distinct compounds can be found in the testimony of the parties' expert witnesses. Three expert witnesses, two provided by Merck, one by Teva, all possessing ordinary skill in the art of chemistry and pharmacology, testified that acid—as that word is ordinarily and customarily used in the relevant art—is distinct in its chemical composition from salt. The term "acid," then, as it is used here, cannot be read to mean "acid and its salts"; the literal scope of the claim can extend only to the acid itself. Because Teva's proposed products are not acids, there can be no literal infringement of the '077 patent.

Nor can there be infringement under the doctrine of equivalents. "[W]hen a patent drafter discloses but declines to claim subject matter . . . this action dedicates that unclaimed subject matter to the public." Johnson & Johnston Assocs. v. R.E. Serv. Co., 285 F.3d 1046, 1054 (Fed. Cir. 2002). Here, the patentee disclosed alendronic acid "and [its] sodium, aniline and lysine salts" but failed to explicitly claim the salts. '077 patent, col. 3, ll. 24-26; id. at col. 16, ll. 43-47. It is a "fundamental principle that claims define the scope of patent protection." Johnson & Johnston, 285 F.3d at 1052. Because the '077 patent does not capture sodium, aniline and lysine salts within the language of the claim, they are dedicated to the public. Therefore, such salts are not equivalent to the alendronic acid literally claimed.

I also disagree with the court's conclusion that the patent is entitled to a term extension. A patent term extension under 35 U.S.C. § 156 extends the life of a patent that claims a method of using a product that has been the subject of regulatory review. The product that was subject to regulatory review here was 4-amino-1-hydroxybutane-1,1-biphosphonic acid monosodium salt trihydrate whereas the patent, as I see it, claims only 4-amino-1-hydroxybutane-1,1-biphosphonic acid. Because the patent does not claim a product that was subject to regulatory review, the patent term extension that was granted for the '077 patent is invalid.

[1] Merck & Co. v. Teva Pharms., USA, Inc., 228 F. Supp. 2d 480 (D. Del. 2002).