United States Court of Appeals for the Federal Circuit

02-1348

GLAXO WELLCOME INC.,

Plaintiff-Appellant,

v.

ANDRX PHARMACEUTICALS, INC.,

Defendant-Appellee.

Stephen B. Judlowe, Morgan Lewis & Bockius LLP, of New York, New York, argued for plaintiff-appellant. With him on the brief were Dennis J. Mondolino, Janet B. Linn, Jason A. Lief, Philip L. Hirschhorn, Esther H. Steinhauer, and Timothy P. Heaton.

Eric D. Isicoff, Isicoff, Ragatz & Koenigsberg, P.A., of Miami, Florida, argued for defendant-appellee. With him on the brief were Teresa Ragatz and Michael D. Bon. Also on the brief were James V. Costigan, Alan B. Clement, and Katherine G. Loving, Hedman & Costigan, P.C., of New York, New York.

Appealed from: United States District Court for the Southern District of Florida

Judge Wilkie D. Ferguson, Jr.

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DECIDED: September 22, 2003

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

NEWMAN, Circuit Judge.

Glaxo Wellcome, Inc. appeals the decision of the United States District Court for the Southern District of Florida, holding on summary judgment that United States Patent No. 5,427,798 (the '798 patent) is valid but not infringed by the bupropion products of Andrx Pharmaceuticals, Inc.[1] We conclude that the district court erred in its construction of the '798 claims. On the correct claim construction, we vacate the summary judgment of noninfringement and remand for further proceedings.

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[1] Glaxo Wellcome, Inc. v. Andrx Pharmaceuticals, Inc., 190 F. Supp. 2d 1354 (S.D. Fla. 2002).

BACKGROUND

The products at issue are the antidepressant medicine having the brand name Wellbutrin[7]SR and the smoking-cessation medicine having the brand name Zyban[7]. The active ingredient of both products is bupropion hydrochloride. Glaxo manufactures and sells sustained release formulations of these products; sustained release extends the medicinal action of the bupropion so that less frequent doses are required, and avoids the surge of bupropion that had occasionally caused seizures upon ingestion. Sustained release formulations must maintain an effective level of the medicine in the bloodstream for an optimum period without unacceptable deviation in pharmacologic activity.

Andrx filed two Abbreviated New Drug Applications (ANDA) seeking approval of generic counterparts of the Glaxo sustained release products, asserting identity of active ingredient and properties with those of Wellbutrin[7]SR and Zyban[7]. Andrx also filed a Paragraph IV certification, asserting that the Andrx products do not infringe the Glaxo '798 patent or that the patent is invalid:

> 21 U.S.C. §355(j)(2)(A) An abbreviated application for a new drug shall contain -
>
> * * *
>
> (vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c) of this section -
>
> * * *
>
> (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted;

The Paragraph IV certification is designed to create a statutory act of infringement, in order to enable adjudication of issues of patent validity and infringement in the absence of actual manufacture, sale, or use of the product:

> 35 U.S.C. §271(e)(2). It shall be an act of infringement to submit -
> (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent,
>
> * * *
>
> if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug or veterinary biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

Glaxo duly filed suit against Andrx for infringement of the '798 patent, in accordance with these statutory provisions.

CLAIM CONSTRUCTION

Appellate review of the district court's claim construction is plenary, see Markman v. Westview Instruments, Inc., 517 U.S. 370, 38 USPQ2d 1461 (1996); Cybor Corp. v. FAS Technologies, Inc., 138 F.3d 1448, 1454-56, 46 USPQ2d 1169, 1172-74 (Fed. Cir. 1998) (en banc), as is our review of the grant of summary judgment. Ecolab, Inc. v. Envirochem, Inc., 264 F.3d 1358, 1363, 60 USPQ2d 1173, 1177 (Fed. Cir. 2001).

The following claims of the '798 patent are representative:

> 1. A controlled sustained release tablet comprising 25 to 500 mg of bupropion hydrochloride and hydroxypropyl methylcellulose,
> the amount of hydroxypropyl methylcellulose to one part of bupropion hydrochloride being 0.19 to 1.1
> and said tablet having a surface to volume ratio of 3:1 to 25:1 cm^{-1}
> and said tablet having a shelf life of at least one year at 59" to 77"F. and 35 to 60% relative humidity,

> said tablet releasing between about 20 and 60 percent of bupropion hydrochloride in water in 1 hour, between about 50 and 90 percent in 4 hours and not less than about 75 percent in 8 hours.
>
> 14. A controlled sustained release tablet comprising an admixture of 100 mg of bupropion hydrochloride and hydroxypropyl methylcellulose which after oral administration of a single one of said tablets in adult men produces plasma levels of bupropion as free base ranging between the minimum and maximum levels as shown in Fig. 5 over twenty-four hours.
>
> 18. A sustained release tablet containing a mixture of (a) 100 mg of bupropion hydrochloride and (b) means for releasing between about 25 and 45% of bupropion hydrochloride in one hour, between 60 and 85% in 4 hours and not less than 80% in eight hours in distilled water said means comprising hydroxypropyl methylcellulose.

In determining the meaning and scope of patent claims, the court gives primary consideration to the specification and the prosecution history, and may consider the prior art and technical treatises and dictionaries. If relevant and helpful, the court may receive the testimony of experts in the field of the invention. See Fed. R. Evid. 702.

The issues of claim construction and infringement focused on the controlled release agent, hydroxypropyl methylcellulose (HPMC). HPMC is defined in the Handbook of Pharmaceutical Additives as follows:

> Definition: Propylene glycol ether of methyl cellulose
>
> Properties: White powd.; swells in water to produce a clear to opalescent visc. colloidal sol'n.; nonionic, insol. in anhyd. alcohol, ether, chloroform; sol. in most polar solvs.
>
> Trade Names: Benecel[7] Hydroxypropyl Methylcellulose; Methocel[7] E3 Premium; Methocel[7] E4M Premium; Methocel[7] E5P; Methocel[7] E6 Premium; Methocel[7] E10MP CR; Methocel[7] E15LV Premium; Methocel[7] E50LV Premium; Methocel[7] E50P; Methocel[7] E Premium; Methocel[7] F4M Premium . . . .

M. & I. Ash, Handbook of Pharmaceutical Additives 552 (1995).

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The specification describes the hydroxypropyl methylcellulose release agent as follows:

> This invention is directed to control sustained release (SR) tablets containing bupropion hydrochloride (as the drug or active ingredient), preferably hydroxypropyl methylcellulose (Methocel[7]) for controlling drug release rate, and cysteine hydrochloride or glycine hydrochloride.
>
> * * *
>
> Methocel[7] is the brand name for hydroxypropyl methylcellulose (HPMC) from Dow Chemical. Other companies also supply HPMC.
>
> * * *
>
> In order to prepare the controlled sustained release (SR) tablets of this invention, particles of bupropion hydrochloride are preferably blended with microcrystalline cellulose and hydroxypropyl methylcellulose (Methocel[7]) to form an admixture of blended powders.
>
> * * *
>
> In the practice of this invention, for every part by weight of bupropion hydrochloride, the amount of hydroxypropyl methylcellulose is 0.19 to 1.1 and more preferably 0.267 to 0.68 parts by weight . . . .

'798 patent, col.1:67 - col.3:14. The specification describes the HPMC used in the examples as follows:

> Hydroxypropyl Methylcellulose 2910, USP used in the examples, conforms to 28.0 to 30.00% methoxyl substitution and 7.0 to 12.0% hydroxypropyl substitution. The preferred nominal viscosity of 2% solution in water is not less than 3,000 centipoise and not more than 5,600 centipoise. It is supplied by Dow Chemical Company, Midland, Mich. as Methocel E4M Premium CR.

'798 patent, col.5:13-20.

During prosecution of the '798 patent, the examiner required that all the claims be limited to hydroxypropyl methylcellulose as the release agent. For example, claim 14, as originally submitted, was as follows:

> 14. A controlled sustained release tablet comprising an admixture of 100mg of bupropion hydrochloride and means for providing a shelf life of at least one year and after oral administration of a single one of said tablets in adult men producing plasma levels of bupropion as free base ranging

substantially between the minimum and maximum levels as shown in Fig. 5 over twenty four hours.

The examiner stated:

> The rate of release is directly related to the release retarding effect of hydroxypropylmethylcellulose. While other excipients have been disclosed, the particular cellulose is considered critical for controlled and/or sustained release and should be incorporated into the independent claims. The disclosure of a single species does not provide a basis for claiming a generic concept.

The applicant acquiesced, and limited all the claims to hydroxypropyl methylcellulose. However, the examiner did not require limiting the hydroxypropyl methylcellulose to any specific grade or molecular weight. What the examiner required was:

> Applicants are claiming a tablet which provides a distinct release profile. The advantages provided by the unique tablet differ from an instant release tablet. The limitations of claims 2-3 are considered critical and should be incorporated into claim 1 for proper enablement.

In response, the applicant amended claim 1 to include the limitations: "said tablet releasing between about 20 and 60 percent of bupropion hydrochloride in water in 1 hour, between about 50 and 90 percent in 4 hours and not less than about 75 percent in 8 hours."

The examiner did not require "a particular grade" of HPMC. The district court erred in holding that the amendment adding the release rate data to the claim limited the claim to the grade of HPMC in the example. The district court stated: "All grades of HPMC could no longer be read into the Glaxo claims to a certainty after the amendment which recognized that a particular grade was critical for controlled or sustained release, therefore an invitation was extended to refer elsewhere for particular grade information." Neither the applicant nor the examiner stated that "a particular grade was critical"; the amendment stated the parameters of the claimed release, not a particular

grade of hydroxypropyl methylcellulose. The HPMC was not limited to the specific example of grade 2910.

Andrx states that its HPMC has a significantly lower molecular weight and viscosity than those of grade 2910, and that the Andrx HPMC does not affect the rate of release because it is readily soluble. Andrx states that it controls the release of bupropion in other ways, not by way of the HPMC in its tablets. Andrx states: "In the Andrx ANDA products, the Eudragit[7]E100/Ethocel[7]100 layer is the release controlling means. This polymer mixture forms a polymeric membrane that regulates the amount of drug that is allowed to release from the pellets by diffusion through the membrane." Andrx also states that its tablets do not exhibit the dissolution and blood plasma profiles required by the claims. Glaxo challenges these statements, pointing out that Andrx was unable to produce a satisfactory controlled release product without using HPMC, and that Andrx has represented to the FDA that its tablets are bioequivalent to the Glaxo tablets, as is required for an ANDA, and thus necessarily match the release rate, dissolution, and blood plasma profiles of the federally approved formulation.

Glaxo states that hydroxypropyl methylcellulose is a polymer and exists in a range of molecular weights, that it is incorrect to construe the claims as limited to a particular grade of hydroxypropyl methylcellulose, and that the specification contains no basis for either a molecular weight or a viscosity limitation. Glaxo argues that while the specification shows the HPMC 2910 (supplied as Methocel[7] E4M Premium CR) that Glaxo used, the description of the invention does not limit the HPMC to a particular grade.

Glaxo states that hydroxypropyl methylcellulose is a gel-forming material known for use in pharmaceutical formulations. There was extensive evidence to this effect. Professor Kathryn E. Uhrich (Rutgers University) testified as follows:

> Significantly, all grades of HPMC are capable of forming a hydrogel that contributes to sustained release when exposed to aqueous media, including the HPMC E5 grade of the Andrx ANDA products. Andrx's products use HPMC E5 and clearly fall within the patented claim element for HPMC. The accused products contain admixtures of HPMC E5 with bupropion and the resulting tablets are sustained release tablets where the HPMC E5 contributes to the release.
>
> * * *
>
> The hydroxypropyl methylcellulose [in the Andrx products] is essential for the sustained or extended release of bupropion hydrochloride as a result of, among other things, the interactions of the hydroxypropyl methylcellulose with the adjacent bupropion/hydroxypropyl methylcellulose, as well as with the other polymers in the formulation during both manufacture and drug release. The hydrophilic properties of hydroxypropyl methylcellulose and its ability to swell in the presence of solvents such as water and certain organic solvents are also important in controlling release. Therefore, in Andrx's proposed 100 mg and 150 mg products, a means for releasing bupropion hydrochloride is hydroxypropyl methylcellulose as required by Claims 18 and 19.

Dr. Banakar, Andrx's expert, described by Andrx as world renowned, testified that a person of ordinary skill in the art of drug formulation reading the '798 patent would understand that hydroxypropyl methylcellulose only includes certain grades of HPMC which are high-viscosity and hydrogel-forming. Dr. Banakar stated:

> If the term "hydroxypropyl methyl cellulose" as used in Claims 1, 14, 15, 18 and 19 of the '798 patent includes low-viscosity, low molecular weight grades of HPMC, then the '798 patent is not enabling of the claimed invention because it does not teach or enable one skilled in the art to make a sustained-release bupropion formulation having the dissolution profiles of Claims 1, 18 or 19 or the blood plasma drug levels of Claims 14 or 15. That is, for a product to exhibit the dissolution profile recited in Claim 1 of the '798 patent, and only require the use of bupropion and HPMC, at the specified ratio, the HPMC must be of a high molecular weight, high-viscosity release-controlling grade. Use of a low-viscosity, low molecular weight soluble grade of HPMC such as the E5 grade at the

> recited ratios without some other sort of release-controlling technology added would make it impossible for one of ordinary skill in the art to obtain the required dissolution profile.
>
> In fact, in order to obtain a suitable sustained release formulation, which uses HPMC E5 as a binding agent and/or seal coat, constituent, Andrx needed to employ a completely different and novel release technology. . . . The Andrx ANDA products do not employ hydrogel technology to control the release of bupropion. Instead, the Andrx ANDA products employ pellets (compressed into a tablet) having certain polymer coatings thereon, which control bupropion release by diffusion.

Dr. Nicholas Peppas (Professor of Pharmacology, Purdue University) described by Glaxo as one of the world's leading scientific experts in hydrogels, disagreed with Dr. Banakar:

> Each of Andrx's products comprises hydroxypropyl methylcellulose and bupropion hydrochloride and the hydroxypropyl methylcellulose is an essential component for the extended and sustained release of bupropion hydrochloride. Its presence in Andrx's formulations and the interactions of the hydroxypropyl methylcellulose with other components inside of this formulation lead to the formation of a gel region in the polymer matrix, which, as I have shown in paragraphs 31, 32 and 36, is a controlling step of the overall release process.
>
> I disagree with Dr. Banakar's opinion [Andrx's expert] with respect to the characteristics of hydroxypropyl methylcellulose and with Dr. Banakar's opinion that a person working in drug formulation or pharmaceutics would interpret Claims 1, 13, 14, 15, 17 and 19 of the '798 patent as limited only to hydroxypropyl methylcellulose grades that form "hydrogels" and would not include "low viscosity grades" of hydroxypropyl methylcellulose. In my opinion, and based on my experience, Dr. Banakar is incorrect in defining "low viscosity" grades of hydroxypropyl methylcellulose as not being "hydrogels."
>
> * * * *
>
> For lower viscosity hydroxypropyl methylcellulose grades, these gels may be somewhat less dense than for higher viscosity hydroxypropyl methylcellulose grades, but the gels formed during swelling definitely control the drug release process in Andrx's products.

Although the expert testimony is facially in conflict, it was not disputed that the mechanism whereby HPMC affects the release of materials with which it is mixed is the swelling of the HPMC in contact with water. It was not disputed that Andrx mixes the

bupropion with HPMC in the interior portion of its tablets. Andrx did not establish that the HPMC it used to mix with the bupropion did not swell in water and affect the rate of release of the bupropion, while arguing that other chemicals affect diffusion. Glaxo stresses that in the Andrx formulation the HPMC is mixed with the bupropion at the core of the tablet, as in the '798 patent.

Andrx in turn stresses that both Andrx and Glaxo use a rapidly soluble grade of HPMC as outer coatings of the tablet. The '798 patent describes the Glaxo outer coating as a thin film of HPMC that does not "substantially affect the release rate of the bupropion hydrochloride from the tablet, since the coating is instant release which rapidly dissolves in the stomach." The '798 specification explains that "because of the nature of the film coating, the release rate will be substantially the same whether or not the tablets are film-coated."

Andrx states that it uses this same grade inside its tablet in admixture with the bupropion, and therefore that it cannot contribute to controlling the rate of bupropion release. Glaxo responds with the testimony of Andrx's formulation scientist, Mr. Jianbo Xie, that he and others at Andrx had been unable to produce a sustained release bupropion product without using HPMC, although they had tried to do so because of the Glaxo patent. By deposition Mr. Xie stated:

> Q: I'm asking what you were thinking when you were doing this development work in the first half of 1997. Whatever the lawyers think or didn't think, weren't you trying to stay away from HPMC to avoid the patents?
>
> A: If we could, we tried to -- how do you say that -- can you repeat your question again?
>
> * * *

Q: You perceived your job so as to stay away from using HPMC if you could so that you could avoid infringement, that is what you were trying to do in early 1997; isn't that correct?
A: Yes, that was a part of the reason, part of the reason.

As a matter of claim construction, the intrinsic and extrinsic evidence lead to the conclusion that the HPMC mixed with the bupropion at the core of the tablet is not limited to a particular grade and molecular weight, provided only that the claimed limitations of release rate and plasma levels are met. When a claim term has an accepted scientific meaning, that meaning is generally not subject to restriction to the specific examples in the specification. CCS Fitness, Inc. v. Brunswick Corp., 288 F.3d 1359, 1366-67, 62 USPQ2d 1658, 1662-63 (Fed. Cir. 2002). It is established that "as a general rule claims of a patent are not limited to the preferred embodiment . . . or to the examples listed within the patent specification." Dow Chemical Co. v. United States, 226 F.3d 1334, 1342, 56 USPQ2d 1014, 1019 (Fed. Cir. 2000); Northern Telecom Ltd. v. Samsung Electronics Co., Ltd., 215 F.3d 1281, 1293, 55 USPQ2d 1065, 1074 (Fed. Cir. 2000) ("preferred embodiments, without more, do not limit claim terms").

In this case the properties and use of hydroxypropyl methylcellulose to control release were well known. The examination record showed that patentability turned on the ratio of the HPMC to the bupropion, the shelf life, the rate of release, the duration of release, and the plasma levels. The hydroxypropyl methylcellulose used in admixture with the bupropion hydrochloride is not limited to the grade and molecular weight of HPMC in the specific examples, but the claims, correctly construed, require that HPMC be present in the stated amount, and that the product have the release rate and duration and plasma levels and other properties set forth in the claims.

INFRINGEMENT

The district court granted Andrx's motion for summary judgment of noninfringement, both literally and under the doctrine of equivalents. The court did not reach Andrx's other defenses; they remain for consideration on remand.

Andrx argues that its release rate is entirely independent of its use of core HPMC, and is controlled entirely by an outer coating containing products branded Eudragit[7] 100 and Ethocel[7] 100, neither of which contains hydroxypropyl methylcellulose. Andrx argues that this formulation is separately patented. Although this fact may be weighed by the district court, particularly if there is an issue of "insubstantial" change with respect to equivalency, separate patentability does not automatically negate infringement. See Atlas Powder Co. v. E.I. DuPont DeNemours & Co., 750 F.2d 1569, 1580, 224 USPQ 409, 417 (Fed. Cir. 1984) ("where defendant has appropriated the material features of the patent in suit, infringement will be found, 'even when those features have been supplemented and modified to such an extent that the defendant may be entitled to a patent for the improvement'") (citation omitted). Whether improvement or modification avoids infringement depends on the particular facts. National Presto Indus., Inc. v. West Bend Co., 76 F.3d 1185, 1191-92, 37 USPQ2d 1685, 1689 (Fed. Cir. 1996). This aspect of infringement could not be resolved adversely to Glaxo on summary judgment, for Glaxo presented substantial evidence that the HPMC as used by Andrx in admixture with the bupropion controls or contributes to the control of release of the bupropion.

Andrx also argues that its release rate and plasma profile are different from those in the Glaxo claims, while Glaxo points out that Andrx has represented the

bioequivalence of its product. This aspect can not be resolved adversely to Glaxo on the summary judgment record, for these material facts were placed in dispute, and were not resolved. See Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 247-50 (1986) (summary judgment is proper when there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law).

The factual issues arising under the doctrine of equivalents were similarly unresolved. In view of our ruling that literal infringement is not limited to a particular grade of HPMC, but that Glaxo must establish that all of the claim limitations are met by the Andrx product, the premise of district court's ruling on equivalency is no longer applicable. Further, that holding was based on the Federal Circuit's decision in Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 234 F.3d 558 (Fed. Cir. 2000) (en banc), which was vacated after the district court's decision. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722 (2002). Thus the district court's decision on this ground is vacated.

CONCLUSION

We conclude that the claims are not limited to a specific grade of hydroxypropyl methylcellulose as used in admixture with the bupropion. The summary judgment of noninfringement is vacated, and the case is remanded for further proceedings.

CLAIMS CONSTRUED, JUDGMENT VACATED, REMANDED