United States Court of Appeals,
Federal Circuit.
In re OMEPRAZOLE PATENT LITIGATION,
Astra Aktiebolag, Aktiebolaget Hassle, KBI-E, Inc., KBI, Inc., Astrazeneca LP,
Astra Pharmaceuticals, LP, Astra Merck Enterprises Inc. and Astra Merck Inc.,
Plaintiffs-Cross Appellants,
v.
Andrx Pharmaceuticals, Inc., Defendant-Appellant,
and
Genpharm Inc., Defendant-Appellant,
and
Cheminor Drugs, Ltd., Reddy-Cheminor, Inc., and Schein Pharmaceutical, Inc.,
Defendants-Appellants,
and
Kremers Urban Development Co. and Schwarz Pharma, Inc., Defendants-Appellees.
Nos. 03-1101 to 03-1106, 03-1131, 03-1132, to 03-1136, 03-1171, 03-1172, 03-1173.

DECIDED: Dec. 11, 2003.
Rehearing and Rehearing En Banc Denied Jan. 23, 2004.

***78** Before RADER, GAJARSA, and PROST, Circuit Judges.

RADER, Circuit Judge.

****1** The United States District Court for the Southern District of New York entered judgment that U.S. Patent Nos. 4,786,505 ('505 patent) and 4,853,230 ('230 patent) are not invalid and are infringed by Andrx Pharmaceuticals, Inc. (Andrx), Genpharm Inc. (Genpharm), and by Cheminor Drugs, Ltd., Reddy-Cheminor, Inc., and Schein Pharmaceutical, Inc. (collectively, Cheminor). *Astra Aktiebolag v. Andrx Pharm., Inc.*, 222 F.Supp.2d 423 (S.D.N.Y.2002). The district court also entered judgment that Kremers Urban Development Co. and Schwarz Pharma, Inc. (collectively, KUDCo) do not literally infringe the '505 and '230 patents. *Id.* Because the district court did not err in its rulings on claim construction, validity, infringement, and evidentiary matters, this court *affirms.*

I.

Astra [FN1] owns the '505 and '230 patents. These patents claim a drug delivery configuration with an enteric coating to protect the active component from stomach acid. These patents appear in the Orange Book listing for the commercial drug Prilosec®, which has omeprazole as the active ingredient. Claim 1 of the '505 patent states:

> FN1. The plaintiffs-cross-appellants are Astra Aktiebolag, Aktiebolaget Hassle, KBI-E, Inc., KBI, Inc., Astrazeneca LP, Astra Pharmaceuticals, LP, Astra Merck Enterprises Inc. and Astra Merck Inc. (collectively, Astra).

> 1. An oral pharmaceutical preparation comprising
> (a) a core region comprising an *effective amount* of a material selected from the group consisting of omeprazole plus an *alkaline reacting compound*, an alkaline omeprazole salt plus an alkaline reacting compound and an alkaline omeprazole salt alone;
> (b) an inert *subcoating* which is soluble or rapidly disintegrating in water disposed on said core region, said *subcoating* comprising *one or more layers of materials* selected from among tablet excipients and polymeric film-forming compounds; and
> (c) an outer layer *disposed on* said subcoating comprising an enteric coating.

'505 patent, col. 16, II. 42-54 (emphases added). Claim 1 of the '230 patent states:

> 1. A pharmaceutical preparation comprising:
> (a) an alkaline reacting core comprising an acid-labile pharmaceutically active substance and an *alkaline reacting compound* different from said active substance, an alkaline salt of an acid labile pharmaceutically active substance, or an alkaline salt of an acid labile pharmaceutically active substance and an alkaline reacting compound different from said active substance;
> (b) an inert *subcoating* which rapidly dissolves or disintegrates in water disposed on said core region, said subcoating comprising *one or more layers* comprising *materials* selected from the group consisting of tablet excipients, ***79** film-forming compounds and alkaline compounds; and
> (c) an enteric coating layer surrounding said subcoating layer, wherein the subcoating layer isolates the alkaline reacting core from the enteric coating layer such that the stability of the preparation is enhanced.

'230 patent, col. 13, II. 1-20 (emphases added).

The generic drug companies Andrx, Genpharm, Cheminor, and KUDCo sought approval from the Food and Drug Administration (FDA) to market omeprazole formulations. Upon filing their Abbreviated New Drug Applications (ANDAs), these

companies certified that the '505 and '230 patents are invalid. Astra responded by suing the generic drug companies for infringement. *See* 35 U.S.C. § 271(e)(2)(A) (2000). The defendants raised various counterclaims, including invalidity.

****2** After a bench trial lasting fifty-two days, the district court issued a 175-page opinion detailing its decision. The district court construed the claims and concluded that the '505 and '230 patents are not invalid and are infringed by the products described in Andrx's, Genpharm's, and Cheminor's ANDA filings. The district court also ruled that the product described in KUDCo's ANDA filing did not infringe the '505 and '230 patents.

Andrx, Genpharm, and Cheminor appeal the validity and infringement rulings. Astra cross-appeals the ruling that KUDCo does not infringe and cross-appeals certain evidentiary rulings. This court has jurisdiction under 28 U.S.C. § 1295(a)(1) (2000).

II.

A court determines patent infringement by first construing the claims and then applying the construed claims to the accused process or product. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976, 34 USPQ2d 1321, 1326 (Fed.Cir.1995) (en banc), *aff'd*, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). This court reviews claim construction without deference. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454, 46 USPQ2d 1169, 1174 (Fed.Cir.1998) (*en banc*). Obviousness is a legal question, reviewed *de novo*, with underlying factual findings reviewed for clear error. *Oakley, Inc. v. Sunglass Hut Int'l*, 316 F.3d 1331, 1339 (Fed.Cir.2003). Anticipation is a question of fact that this court reviews for clear error. *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1458 (Fed.Cir.1984). This court reviews a district court's evidentiary rulings for abuse of discretion. *Kearns v. Chrysler Corp.*, 32 F.3d 1541, 1547 (Fed.Cir.1994).

A. Claim Construction

Andrx, Genpharm, and Cheminor challenge the district court's construction of the terms "alkaline reacting compounds" (ARCs), "subcoating," "disposed on," "materials," "effective amount," and "pH buffering alkaline compound." Astra cross-appeals for a broader construction of "alkaline reacting compounds."

This court affirms the district court's claim construction in all respects. The district court correctly construed "alkaline reacting compound" to mean "(1) a pharmaceutically acceptable alkaline, or basic, substance having a pH greater than 7 that (2) stabilizes the omeprazole or other acid labile compound by (3) reacting to create a micro-pH of not less than 7 around the particles of omeprazole or other acid labile compound." *Astra*, 222 F.Supp.2d at 453. That construction flows from the following definition in the patents: "an alkaline reacting, otherwise inert, ***80** pharmaceutically acceptable substance (or substances), which creates a 'microp H' around each omeprazole particle of not less than pH = 7." '505 patent, col. 3, II. 38- 44; '230 patent, col. 8, II. 36-40. This court perceives no error in this construction.

The district court correctly construed "subcoating" as "a layer that is physically on and conforms to the contours of a core and is underneath another layer--the enteric coating ... [wherein] ... subcoatings and gelatin capsules are different species of the generic term 'separating layer.' " By choosing the term "coating," the applicant identified a covering that conforms to the shape of the underlying core. The specifications use the term "separating layer" in connection with the claim term "subcoating." This description of the function of subcoating, however, does not expand the term to embrace any layer that separates the core from the surrounding environment. "Separating layer" refers only to the function of the form-fitting cover, with little information about the structure that supplies the separation. The patents do not otherwise define "separating layer" and "subcoating" or even "coating." Finally, the district court gave due weight to the fact that during prosecution of the '505 patent before the United States Patent and Trademark Office (PTO), Astra distinguished a reference that disclosed a gelatin capsule between a core and an enteric coating. *Astra*, 222 F.Supp.2d at 465-66.

****3** The district court correctly construed "disposed on" because nothing in the context or meaning of the term provides limitations beyond a reference to the layer's location. "Disposed on" does not specify any method or structure involved in application of the subcoating.

As to the term "materials" defining the subcoating, the district court reached the correct construction by placing the term in its proper context. The claims recite "one or more layers of materials" ('505 patent) and "one or more layers comprising materials" ('230

patent). The use of the plural "materials," as the district court notes, represents an effort to match the tense of "layers." In other words, the plural term does not necessarily require multiple compositions, but instead reflects an attempt to achieve grammatical consistency. This court finds no support in the intrinsic evidence for a narrower interpretation that would exclude a subcoating of only one material. This term therefore does not exclude subcoatings of only one material.

As to "effective amount," this court rejects Astra's argument that the ARC is a simple excipient and thus "effective amount" only applies to omeprazole. "Excipient" is defined as a "pharmacologically inert, adhesive substance, as honey, syrup, or gum arabic, used to bind the contents of a pill or tablet." Random House Webster's Unabridged Electronic Dictionary (1996). The ARC is not an inert adhesive, and thus does not fit within that definition. Instead, the ARC is alkaline and reacts to stabilize the active drug. The district court thus correctly construed "effective amount" as limiting both the drug component and the ARC.

In construing the term "pH buffering alkaline compound," the district court reasoned as follows:

> [T]he terms "pH-buffering compound" and "pH-buffering alkaline reacting compound" are used interchangeably with the term "alkaline reacting compound" throughout the patent. (See Lovgren Tr. 4477:21-4478:5 ("I think an average skilled formulator reading this patent will see these terms used interchangeably so many times in the specifications.").) ***81** The person of ordinary skill in the art would, therefore, understand that the term "pH-buffering" generally was not used in the patent to convey the traditional characteristics of a buffer in chemistry.

Astra, 222 F.Supp.2d at 478. Given the context of the patents and the supporting testimony in the record, this court affirms this reasoning.

Finally, the district court may have harmlessly erred by reading *AFG Industries, Inc. v. Cardinal IG Co.*, 239 F.3d 1239 (Fed.Cir.2001), to justify a "substantially" addition to claim limitations. The district court's comment, *Astra*, 222 F.Supp.2d at 460, which arguably overstates matters, does not affect the trial court's definition of the limitations and their effect on the infringement analysis. The district court simply used the premise to support a claim construction that this court concludes was correct independent of this aspect of the district court's analysis.

B. Validity

****4** Appellees contend that the claims are invalid as anticipated by prior art disclosing a formulation with a gelatin capsule as an intermediate layer. This anticipation argument hinges on construing the claims to include a gelatin capsule as a subcoating. This court has rejected that construction, and therefore affirms the district court's ruling on anticipation.

The obviousness arguments rely on European Patent Office (EPO) patent application 0 124 495 (EP '495), British patent application no. 760,403 (GB ' 403), U.S. Patent No. 4,335,099 ('099 patent), Shin-Etsu Chemical Co. brochure TC-5, and Hager's Handbuch der Pharmazeutischen Praxis (Hager's Handbook). The district court found that the TC-5 and Up-to-Date references were not available to the public and thus are not "printed publications." *Astra*, 222 F.Supp.2d at 575-578. "Whether an asserted anticipatory document qualifies as a 'printed publication' under § 102 is a legal conclusion based on underlying factual determinations." *N. Telecom. Inc. v. Datapoint Corp.*, 908 F.2d 931, 936 (Fed.Cir.1990).

Genpharm does not argue that Up-to-Date is a printed publication. Instead, Genpharm cites *Thomas & Betts Corp. v. Litton Sys. Inc.*, 720 F.2d 1572, 1580-81 (Fed.Cir.1983) for the premise that Up-to-Date can be used to show the level of skill in the art. Genpharm reads too much into *Thomas & Betts* because, unlike here, the document at issue in that case received additional support in the form of testimony about the state of art at the time of the publication. The level of skill in the art is a factual question, and the district court did not clearly err in declining to consider the Up-to-Date disclosure as reflecting the level of skill in the art.

Cheminor relies on Astra's statement, while prosecuting the '230 patent before the EPO, that TC-5 is a "general publication promoting the use of TC-5." But that statement does not unambiguously state that TC-5 was a "generally available" publication, as required for a printed publication. The statement could also refer to the nature of what TC-5 discloses, not the breadth of its availability or dissemination. The district court did not clearly err in finding that Cheminor did not adequately account for differences in the legal requirements for prior art in the U.S. and Europe. Cheminor also relies on Astra's statement while prosecuting the '230 patent in South Africa,

that TC-5 is "relevant prior art." Here again, Cheminor did not adequately account for differences in the ***82** legal requirements for prior art in the U.S. and South Africa.

Hager's Handbook discloses that sensitive cores "must be precoated with non-reactive underlayers." The district court correctly dismissed this as "cumulative to the other general, vague statements" in other proffered documents, particularly because Hager says nothing about the other limitations of subcoating (b), such as water solubility and composition. *Astra*, at 590. The district court did not clearly err in reaching this conclusion.

****5** EP '495 discloses a formulation that includes an enteric coating and a core containing a salt of omeprazole. EP '495 suggests putting cores in soft gelatin capsules covered with an enteric coating. The district court found that GB '403 and the '099 patent provide no motivation to add a subcoating. The district court did not clearly err in concluding that GB '403, which refers to "sub-coating with a compatible material" a drug that "has a highly alkaline pH," is not specific enough. The '099 patent discloses an enteric-coated lgA/delta-globulin formulation with a water-soluble PVP subcoating (Example 3). Nothing in the '099 patent explains the purpose of the subcoating. The '099 patent thus would not inform a person of ordinary skill in the art that such a subcoating is useful for omeprazole formulations.

C. Infringement

Genpharm relies exclusively on error in claim construction and does not allege other error in the district court's infringement ruling. Because this court affirms the district court's claim construction, Genpharm's noninfringement argument necessarily fails.

Apart from alleging error in claim construction, Cheminor argues only that Astra has not shown that Cheminor's product satisfies the requirement for a microenvironment pH. Cheminor did no testing, and presents no data or expert testimony to rebut Astra's evidence. In fact, Cheminor's own expert, Dr. Ravinder, gave testimony that supports Astra's position. Dr. Ravinder stated that "the pH is the result of the combination of excipients present in the core region" and answered "yes" when asked whether Cheminor's core region provides an alkaline environment for omeprazole. Further, Cheminor's tests showed that the core region of its product has a pH of about 9. This supports the results of Astra's expert Dr. Davies showing that microenvironments around the omeprazole particles have a pH of about 9. In light of the record evidence, the district court did not clearly err in finding that the meglumine included in the core provides a micro-pH greater than 7 around the active ingredient and that Cheminor's product infringed.

Andrx, in contrast to Genpharm and Cheminor, does not directly add a subcoating in preparing its formulation. Nevertheless, the district court found that the core bears a subcoating that is a water-soluble polymeric film made of a salt of HPMCP, [FN2] formed by reaction between disodium hydrogen phosphate (DHP) in the core and HPMCP in the enteric coating layer of Andrx's formulation. The district court analyzed at length the record evidence, *Astra*, 222 F.Supp.2d at 529-40, and this court discerns no clear error in the district court's conclusion. Specifically, Dr. Davies tested Andrx's formulation and testified that the ATR-FTIR spectra confirmed the presence of HPMCP salt between ***83** the enteric coating and the core. That fluorescing layer between the core and the enteric coatings was HPMCP salt. The district court also considered tests performed by Andrx's expert Dr. Gardella, but found that because those tests were only done on core pellets and not on Andrx's enteric-coated formulation, it could not credit Dr. Gardella's opinions. *Id.* at 533 n. 69, 534-35.

FN2. HPMCP is hydroxypropyl methylcellulose.

****6** Andrx contends that Astra provided no evidence that the alleged subcoating was soluble or rapidly disintegrates in water. Rather, Andrx argues that nearly half of the subcoating was talc and that Astra conceded that talc is insoluble. Andrx further asserts that Astra did not test any material containing talc for solubility. The claims require only that the subcoating "rapidly disintegrates in water." The district court credited evidence that insoluble particles within an otherwise soluble film material do not necessarily prevent the overall film from disintegrating in water. The trial court found it reasonable to infer that if the film-forming component of a film dissolves, the film disintegrates. The record evidence supports the district court's finding that a film of HPMCP salt containing large amounts of talc would disintegrate in water. Dr. Davies's test data and testimony showed that the HPMCP salt is film-forming and rapidly dissolves in water. In addition, GB '403 discloses that a

formulation with a cellulose-based enteric coating with 50% talc disintegrates in water-based artificial intestinal fluid. GB ' 403, p. 3, II. 83-85; p. 4, II. 1-4 and 66-70.

Thus, the record does contain evidence to support the district court's conclusion that Astra showed that the subcoating rapidly disintegrates in water. Andrx provided no contrary tests to rebut the evidence that Astra supplied on this point. For infringement, the record need only reflect proof by preponderant evidence. Here, the district court did not clearly err in finding that Astra supplied preponderant evidence of infringement. Thus, the standard of review on this question resolves the question in favor of the district court's determination. This court affirms.

Considered in proper context, Astra did not concede that the talc in Andrx's formulation defeats infringement. Astra's comments merely reflect its general observations about talc in isolation, not as part of a HPMCP salt film as it appears in the Andrx formulation. Moreover, the patent specifications disclose that the separating layer may contain talc. '505 patent, col. 4, II. 54-56, '230 patent, col. 9, II. 48-50. In any event, the preponderance of evidence in the record supports the trial court's finding after careful exploration of the topic in a lengthy trial.

Astra cross-appeals the district court's ruling that KUDCo does not infringe. The district court found that Astra "failed to put forward sufficient evidence ... to prove ... that KUDCo's product, including the HPMC contained therein, contains an ARC." Astra contends that the HPMC in KUDCo's formulation contains an alkaline material that satisfies the ARC limitation. Still, Astra identifies no ARC in the core. Instead, Astra contends that it suffices to show pH > 7 in regions "immediately around or in close proximity to the omeprazole particles." From this showing, Astra would infer an ARC in the core. This court disagrees, because the claims plainly require an ARC. The district court did not clearly err in finding that Astra's data is inadequate to show that KUDCo's formulation contains an ARC in the core.

***84** D. Evidentiary Rulings

****7** Astra also contends that the district court erred by allowing KUDCo to present evidence supporting its "size-reduction step" non-infringement theory, and by excluding Astra's expert testimony in rebuttal. Because the district court provided a well-reasoned basis for those rulings, see *Astra* at 552 n. 82, the district court did not abuse its discretion.