United States Court of Appeals for the Federal Circuit

06-1118

ABRAXIS BIOSCIENCE, INC. (formerly known as
ASTRAZENECA PHARMACEUTICALS LP
and ASTRAZENECA UK LTD.),

Plaintiffs-Appellees,

v.

MAYNE PHARMA (USA) INC.
(formerly known as Faulding Pharmaceutical Company),

Defendant-Appellant.

Denise L. Loring, Ropes & Gray LLP, of New York, New York, argued for plantiffs-appellees. With her on the brief were Sona De and Herbert F. Schwartz; and Robert J. Goldman, of Palo Alto, California.

Charles A. Weiss, Kenyon & Kenyon LLP, of New York, New York , argued for defendant-appellant. With him on the brief were Thomas J. Meloro and Richard L. DeLucia. Of counsel on the brief was Jules E. Goldberg, Reed Smith, LLP, of New York, New York.

Appealed from: United States District Court for the Southern District of New York

Judge William H. Pauley, III

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ABRAXIS BIOSCIENCE, INC. (formerly known as
ASTRAZENECA PHARMACEUTICALS LP
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Defendant-Appellant.

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DECIDED: November 15, 2006

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Before LOURIE, Circuit Judge, PLAGER, Senior Circuit Judge, and RADER, Circuit Judge.

LOURIE, Circuit Judge.

Mayne Pharma (USA), Inc. ("Mayne") appeals from the decision of the United States District Court for the Southern District of New York granting judgment of infringement of U.S. Patents 5,714,520 ("the '520 patent"), 5,731,355 ("the '355 patent"), and 5,731,356 ("the '356 patent"), both literally and under the doctrine of equivalents, in favor of AstraZeneca Pharmaceuticals LP and AstraZeneca UK Ltd. (collectively "AstraZeneca"). AstraZeneca Pharms. LP v. Mayne Pharma (USA) Inc., No. 02-7936, 03-6487 (S.D.N.Y. Nov. 2, 2005) ("Nov. 2, 2005 Opinion"). Because the district court erred in its construction of "edetate," which was the basis upon which it found literal infringement, we reverse the court's claim construction and the court's finding of literal

infringement. However, because the court did not clearly err in determining that the accused product infringes under the doctrine of equivalents, we affirm the district court's judgment.

BACKGROUND

In November 1989, AstraZeneca launched in the United States an original pharmaceutical composition used to induce and maintain general anesthesia and sedation in patients. The product was marketed and sold under the trade name DIPRIVAN® for treatment in humans and RAPINOVET® for veterinary use. The composition consists of an injectible oil-in-water emulsion containing propofol, or 2,6-diisopropylphenol, as its active ingredient.

Typically, DIPRIVAN® is administered to patients by infusion, which involves the use of a "giving set." '520 patent, col.2 ll.56-61. A giving set involves connecting a reservoir containing the propofol emulsion with the patient's vein via the appropriate tubing. In 1990, AstraZeneca became aware that patients using DIPRIVAN® were increasingly suffering from post-operative infections. It was determined that the infections were linked to the microbial contamination of fluids contained in the DIPRIVAN® giving set. As a result, the Food and Drug Administration ("FDA") imposed a requirement that the giving sets be "changed at least every 6 or 12 hours dependent on the presentation being used." Id., col.3 ll.2-3.

AstraZeneca researchers began developing an improved formulation that would allow giving sets to be changed less frequently. The inventors of the patents in suit recommended the use of preservatives in DIPRIVAN®. They experimented with a number of preservatives, but discovered that most were ineffective. The inventors

ultimately discovered that one preservative in particular, disodium edetate, was unexpectedly effective in retarding microbial growth in the propofol formulation without disrupting the oil-in-water emulsion for at least twenty-four hours. AstraZeneca subsequently developed an improved version of the original DIPRIVAN® formulation consisting of edetate, as well as all of the ingredients in the original formulation. The original DIPRIVAN® formulation and the improved formulation have identical anesthetic properties. Nov. 2, 2005 Opinion, slip op. at 4.

In March 1995, the inventors applied for a patent on their improved DIPRIVAN® formulation. In December 1995, AstraZeneca also filed a supplemental New Drug Application ("NDA") on the new formulation. It was approved on June 11, 1996, and AstraZeneca was granted three years of marketing exclusivity for the improved DIPRIVAN® formulation. AstraZeneca also requested the FDA to withdraw approval on the original DIPRIVAN® formulation, and in 1998, the FDA granted the request.

Abraxis Bioscience, Inc. ("Abraxis") is the assignee of the three asserted patents that cover the improved formulation.[1] The '520 patent, entitled "Propofol Composition Containing Edetate," was issued on February 3, 1998. The '355 and '356 patents, both entitled "Pharmaceutical Compositions of Propofol and Edetate," were issued on March 24, 1998 from divisional applications based on the '520 patent application. All three patents share a common specification. The asserted claims of the patents are claims 1-14, 16-32, and 34 of each patent, as well as claims 38 and 39 of the '520 patent.

[1] On August, 11, 2006, Abraxis was substituted as plaintiff-appellee in this action for AstraZeneca after acquiring all rights, title, and interest in the '520, '355, and '356 patents and NDA No. 19-627.

In 1995, scientists at ESI Lederle ("ESI") learned of the reports of infection relating to original DIPRIVAN®.[2] ESI also learned that AstraZeneca reformulated its composition by adding an antimicrobial agent, and decided to develop a similar generic formulation. Dr. Martin Joyce of ESI led those development efforts. After reviewing AstraZeneca's '520 patent, Dr. Joyce and his colleagues screened antimicrobial agents in an effort to replace the edetate in the improved DIPRIVAN® formulation with a different agent. Id., slip op. at 8-9. Dr. Mary George, a senior formulator at ESI, advised the formulation group that the calcium trisodium salt of diethylenetriaminepentaacetic acid (pentetate), which is also referred to as DTPA, was a promising candidate as an antimicrobial agent.[3]

In selecting that compound, Dr. George considered a number of factors. Dr. George stated in a memorandum that the "product must be approvable as an ANDA without clinical or safety studies . . . [and] must match the reference product characteristics and stability profile" of AstraZeneca's improved formulation. J.A. at A3662. Dr. George also noted that since calcium trisodium DTPA is "structurally similar to edetate, product stability is predicted to be unaffected." Id. ESI determined that calcium trisodium DTPA produced the same characteristics and stability profile as

[2] Abbreviated New Drug Application ("ANDA") No. 76-452 relates to the generic propofol emulsion. ESI, a division of Wyeth Pharmaceuticals, Inc. ("Wyeth"), originally filed this ANDA and was the party responsible for developing the generic formulation. Baxter Healthcare Corporation subsequently acquired ESI from Wyeth, as well as the generic propofol product. Mayne acquired the application from Baxter and became the applicant of record for ANDA No. 76-452. Mayne was substituted as defendant in this action for Wyeth and ESI on February 3, 2003.

[3] Throughout this opinion, we will refer to this compound as calcium trisodium DTPA.

improved DIPRIVAN®. Nov. 2, 2005 Opinion, slip op. at 9. Ultimately, calcium trisodium DTPA was chosen as the final antimicrobial additive.

ESI filed a patent application on its pharmaceutical composition and was later granted U.S. Patent 6,028,108 ("the '108 patent") on February 22, 2000. On June 28, 2002, ESI filed ANDA No. 76-452 on its generic propofol formulation. ESI included a Paragraph IV Certification asserting that the patents in suit were invalid, unenforceable, or would not be infringed by its generic propofol formulation. Pursuant to 21 U.S.C. § 355(j)(2)(B)(ii), Wyeth notified AstraZeneca by letter dated August 20, 2002 that it was seeking FDA approval for its generic propofol formulation and that it intended to commercially manufacture, use, or sell a 20 ml vial product. AstraZeneca filed the first of two patent infringement actions against Wyeth and ESI on October 4, 2002. Thereafter, Mayne, as the indirect assignee of ESI, sent AstraZeneca a notice letter dated July 15, 2003 informing AstraZeneca of its intent to commercially manufacture, use, or sell its generic propofol formulation in 50 ml and 100 ml vials. AstraZeneca initiated the second lawsuit based on this notice letter, and both actions were consolidated.

The district court issued a Markman ruling on December 28, 2004. AstraZeneca Pharms. LP v. Mayne Pharma (USA), Inc., 352 F. Supp. 2d 403 (S.D.N.Y. 2004). The court construed three contested terms. Only one term, "edetate," is at issue in this appeal. This term was construed by the district court as "EDTA as well as compounds structurally related to EDTA regardless of how they are synthesized." Id. at 417. After holding an eleven-day bench trial, the court entered judgment in favor of AstraZeneca, concluding that the filing of Mayne's ANDA No. 76-452 infringed the asserted claims of

the patents in suit. Based on the district court's construction of "edetate" as encompassing structural analogs of EDTA, the court found that Mayne's generic propofol formulation literally infringed claims 1 and 3-14 of the asserted patents, and claim 38 of the '520 patent. Additionally, the court determined that Mayne's formulation infringed claims 1-14, 16-32, and 34 of the asserted patents, and claims 38 and 39 of the '520 patent under the doctrine of equivalents. Mayne timely appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

Claim construction is an issue of law, Markman v. Westview Instruments, Inc., 52 F.3d 967, 970-71 (Fed. Cir. 1995) (en banc), that we review de novo. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc). The district court's determination of infringement, in contrast, is a question of fact that we review for clear error. Centricut, LLC v. Esab Group, Inc., 390 F.3d 1361, 1367 (Fed. Cir. 2004). A determination of infringement requires a two-step analysis. "First, the court determines the scope and meaning of the patent claims asserted, and then the properly construed claims are compared to the allegedly infringing device." Cybor, 138 F.3d at 1454 (citations omitted). "A 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).

I.
Claim Construction

Central to the disposition of this appeal is the construction of the term "edetate," which is a limitation in each of the asserted claims. Claim 1 of the '520 patent is a representative claim. It reads, in pertinent part, as follows:

> 1. A sterile pharmaceutical composition for parenteral administration which comprises an oil-in-water emulsion in which propofol dissolved in a water-immiscible solvent, is emulsified with water and stabilized by means of a surfactant, and which further comprises an amount of edetate sufficient to prevent a no more than 10-fold increase in growth of each of Staphylococcus aureus ATCC 6538, Escherichia coli ATCC 8739, Pseudomonas aeruginosa ATCC 9027 and Candida albicans ATCC 10231 for at least 24 hours as measured by a test . . . .

'520 patent, col.11 ll.33-41 (emphasis added).

The district court construed "edetate" as "EDTA as well as compounds structurally related to EDTA regardless of how they are synthesized." AstraZeneca, 352 F. Supp. 2d at 417. In construing "edetate," the court noted that the patentees defined "edetate" in the specification as "EDTA and derivatives thereof." '520 patent, col.4 ll.51-52. The court proceeded to define the term "derivatives" by adopting a broad definition, specifically one that encompasses structural analogs of EDTA as well as synthetic derivatives.[4] The district court found that that broad definition of "derivatives," and thus "edetate," was most consistent with the use of the term in the specification.

[4] Relying on the declaration of Michele M. Winneker, the court stated that a structural analog is "a compound that has the same structural components as the lead compound," even if it cannot practically be prepared from that lead compound. AstraZeneca, 352 F. Supp. 2d at 414 n.6. The court further stated that a synthetic derivative, in contrast, is a compound that "is synthesized from that lead compound" by one or more chemical reactions. Id.

Mayne argues that the district court erred by adopting an overly broad definition of "edetate," particularly by including structural analogs as "derivatives." Mayne contends that that definition is unsupported by the intrinsic evidence. Mayne asserts that based on the intrinsic evidence, the correct construction of "edetate" is "the salts or anions of EDTA."

Abraxis responds that the district court correctly construed "edetate" to include structural analogs of EDTA. In defining the term "derivatives," Abraxis asserts that the district court properly adopted the broader definition, particularly in light of certain statements in the specification.

"Words of a claim 'are generally given their ordinary and customary meaning.'" Phillips v. AWH Corp., 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc). A patentee, however, can "act as his own lexicographer to specifically define terms of a claim contrary to their ordinary meaning." Chef Am., Inc. v. Lamb-Weston, Inc., 358 F.3d 1371, 1374 (Fed. Cir. 2004) (citation omitted). To a person of ordinary skill in the art, the term "edetate" can refer to the common name of an EDTA salt, namely, a salt of ethylenediaminetetraacetic acid.[5] J.A. at A6624. That term could also refer more generally to "[a]ll anions derived from [EDTA]." Id. at A6796. As the district court properly concluded, however, the patentees acted as their own lexicographers by defining "edetate" in the specification. In particular, the patentees stated that: "By the term 'edetate' we mean ethylenediaminetetraacetic acid (EDTA) and derivatives thereof . . . ." '520 patent, col.4 ll.51-52. The district court correctly noted that a plain reading of that statement indicates that "edetate" includes "EDTA and derivatives of EDTA."

[5] As noted in the specification, EDTA stands for ethylenediaminetetraacetic acid. '520 patent, col. 4 ll. 51-52.

AstraZeneca, 352 F. Supp. 2d at 413 (citing Webster's Third New International Dictionary 2372 (1993) for the definition of "thereof"). We disagree, however, with the district court's definition of "derivatives." Under the district court's construction, structural analogs of EDTA fall within the literal scope of the claim. The intrinsic evidence, however, fails to support that conclusion.

As this court recognized in Phillips, "claims 'must be read in view of the specification, of which they are a part.'" 415 F.3d at 1315 (quoting Markman, 52 F.3d at 979). We further stated that "the specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" Id. (internal citations omitted). Here, the specification leads us to the conclusion that the patentees intended a more narrow meaning for the term "derivatives" than the definition adopted by the district court.

We first note that the part of the specification describing "edetate" reads:

> By the term "edetate" we mean ethylenediaminetetraacetic acid (EDTA) and derivatives thereof, for example the disodium derivative is known as disodium edetate. In general suitable edetates of this invention are those salts having lower affinity for EDTA than calcium. Particular derivatives of use in the present invention include trisodium edetate, tetrasodium edetate and disodium calcium edetate.

'520 patent, col.4 ll.51-57 (emphases added). Thus, the inventors listed several derivatives of EDTA that are suitable for the invention. Notably, all of these derivatives are salts of EDTA, none are structural analogs.

Abraxis argues, and the district court agreed, that the EDTA salts merely serve as examples of "derivatives" and thus "may not be used to limit a claim term." AstraZeneca, 352 F. Supp. 2d at 413. We disagree. When reading these statements in

the context of the entire specification, it is evident that the listing of various EDTA salts defines the term "derivatives." At the very least, "derivatives" does not include structural analogs.

Earlier in the specification, the patent discloses that considerable effort had been spent experimenting with a number of known preservatives including, among others, benzyl alcohol, sodium methyl hydroxybenzoate, sodium metabisulphite, and sodium sulphite. '520 patent, col.4 ll.22-28. The patentees noted that none of those preservatives met their requirements. Instead, after extensive experimentation, the universe of potential antimicrobial agents was narrowed down to one particular agent, i.e., edetate. The patentees explained:

> We then investigated the possible use of other agents which might have the action that we sought. We unexpectedly found that edetate, which is not regarded as a broad spectrum antimicrobial agent was the only agent that would meet our requirements.

Id., col.4 ll.28-33 (emphasis added). That statement indicates that edetate possessed particular chemical properties that allowed it to work as an effective antimicrobial agent and that the term "derivatives" was not intended to extend broadly.

The patentees further proceeded to describe their experimentation. They noted:

> As can be seen from the experimental section, sodium calcium edetate has some advantages over other additives but disodium edetate is exceptional. Accordingly, most preferably the edetate is disodium edetate.

Id., col.4 ll.64-67 (emphases added). That statement again emphasizes the significance of the patentees' discovery that edetate, or more particularly EDTA salts, worked as successful antimicrobial agents. Notably, in the experimental section which that statement references, the patent lists five different agents including sodium

metabisulphite, sodium sulphite, hydroxybenzoates, sodium calcium edetate, and disodium edetate dehydrate. As noted above, three of those agents had already been rejected by the patentees as suitable agents. Significantly, the two remaining agents, sodium calcium edetate and disodium edetate dehydrate, which the patentees described as advantageous, preferable and "exceptional," are EDTA salts.

We thus conclude that the listing of EDTA salts as "[p]articular derivatives of use in the present invention," coupled with the statements regarding the uniqueness of edetate as the only successful antimicrobial agent, and the patentees' description of EDTA salts as advantageous, preferable, and "exceptional," limit the term "derivatives" to EDTA salts or compounds that maintain the EDTA free acid structure. Those statements are inconsistent with a definition of "derivatives" that includes structural analogs that can encompass a large number of non-derivative compounds. That definition fails to recognize that the patentees' discovery focused on the unexpected effectiveness of edetate and its salts as antimicrobial agents.

Abraxis argues that a narrow definition is unsupported by the specification, particularly in light of the patentees' statement that "[t]he nature of the edetate is not critical, provided that it fulfils the function of preventing significant growth of microorganisms for at least 24 hours in the event of adventitious extrinsic contamination." Id., col.4 ll.57-61. But, when read in context, that statement does support a narrow construction. It appears in the specification directly after the listing of the various EDTA salts that the patentees identified as suitable edetates. Thus, the statement that the "nature of the edetate is not critical" only connotes that the choice of which particular agent to use, i.e., EDTA or any EDTA salt, itself is not of critical

importance, as long as the agent chosen can adequately prevent microbial growth. Contrary to Abraxis' suggestion, that sentence does not support a broad construction for "derivatives."

Abraxis also relies on another statement in the specification in support of its definition for "derivatives." Abraxis points to the patentees' use of the term "derivatives" in the context of silicone. The patent identifies "dimethicone" and "simethicone" as "silicone derivative[s]." Id., col.3 ll.40-41. Those compounds are not synthetic derivatives of silicone, but are structural analogs. Abraxis contends that using the term in that manner to broadly describe a class of antifoaming agents supports a broader definition for "derivatives" in the context of "edetate." We disagree. That term was used to describe a general class of antifoaming agents as disclosed in another patent. That is far removed from the pointed discussion in the specification identifying the "derivatives" of "edetate." Thus, the passing reference to silicone derivatives fails to overcome our conclusion that the patentees narrowly defined edetate "derivatives" to mean EDTA and its salts.

In light of the foregoing analysis, despite the district court's thorough analysis and review of the patent, we conclude that the district court erred by adopting a broad definition of the term "derivatives." Based on the specification, "derivatives" does not include structural analogs. Accordingly, the proper construction of "edetate" is EDTA and derivatives of EDTA, such as salts, but not including structural analogs.

II.
Literal Infringement

Having determined the correct claim construction of "edetate," we next consider literal infringement. Literal infringement requires that each and every claim limitation be

present in the accused product. Frank's Casing Crew & Rental Tools, Inc. v. Weatherford Int'l, Inc., 389 F.3d 1370, 1378 (Fed. Cir. 2004). All of the asserted claims require "edetate," i.e., EDTA or derivatives of EDTA. Thus, the issue before the court is whether calcium trisodium DTPA is a derivative of EDTA.

As Abraxis conceded during oral argument, DTPA is not a derivative of EDTA since it cannot be synthesized from EDTA in a laboratory, and it is certainly not a salt of EDTA. Abraxis' expert admitted that synthesizing DTPA from EDTA cannot be performed in a laboratory, but stated that it "can easily be done on the blackboard." J.A. at A727. However, theoretical blackboard constructs do not necessarily make a structural analog a derivative. Abraxis itself conceded that DTPA is only a structural analog of EDTA, and thus qualified only as an EDTA "derivative" under the district court's claim construction. Consequently, in light of our claim construction and Abraxis' own admissions, we conclude that the district court was clearly erroneous in finding that Mayne's product literally infringes the asserted claims of the patents in suit, because neither EDTA nor any of its salts or derivatives is present in the accused formulation.

III.
Doctrine of Equivalents

Unlike claim construction, a matter of law reviewed de novo, infringement under the doctrine of equivalents is a factual determination that we review for clear error. Centricut, LLC v. Esab Group, Inc., 390 F.3d 1361, 1367 (Fed. Cir. 2004). Thus, notwithstanding our disagreement with the district court's conclusions regarding claim

construction and literal infringement, we will affirm its decision on infringement under the doctrine of equivalents.[6]

"Infringement may be found under the doctrine of equivalents if every limitation of the asserted claim, or its 'equivalent,' is found in the accused subject matter, where an 'equivalent' differs from the claimed limitation only insubstantially." Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp., 149 F.3d 1309, 1315 (Fed. Cir. 1998). An accused device that "performs substantially the same function in substantially the same way to obtain the same result" as the patented invention may infringe under this doctrine. Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 608 (1950).

On appeal, Mayne advances three main arguments in support of its position that the court clearly erred in finding that calcium trisodium DTPA is an equivalent of edetate. First, Mayne argues that the court clearly erred in its analysis with regard to the "way" prong of the function-way-result test by improperly defining the "way" in which edetate works. Secondly, Mayne argues that it was impermissible as a matter of law for the meaning of edetate to extend to calcium trisodium DTPA by equivalence because the patentees chose to narrowly claim their invention. According to Mayne, the patentees chose to use the restrictive term "edetate" in claiming their invention, rather than broader terms such as "polyaminocarboxylates" or "metal ion chelators," and thus are now precluded from extending patent protection to cover compounds beyond

[6] While our modified claim construction directly affects the outcome of our literal infringement analysis, the outcome of the doctrine of equivalents issue is not similarly affected, as discussed below.

edetate.[7] Third, Mayne asserts that the lack of known interchangeability between calcium trisodium DTPA and edetate as an antimicrobial agent indicates that the substitution of calcium trisodium DTPA is a "substantial" change weighing against a finding of equivalence.

Abraxis responds that the district court properly analyzed the differences between edetate and calcium trisodium DTPA under the function-way-result test, and correctly determined that the differences between them are insubstantial, and thus the two are equivalent. Secondly, Abraxis argues that it is not estopped from asserting that calcium trisodium DTPA is an equivalent of edetate. Lastly, Abraxis asserts that the known interchangeability of one element for another is just one of several factors to be considered in a doctrine of equivalents analysis. According to Abraxis, the district court correctly found that that factor was insufficient to outweigh the substantial evidence supporting the conclusion that edetate and calcium trisodium DTPA are equivalent.

In a well-reasoned opinion, the district court concluded that calcium trisodium DTPA and edetate were equivalent after finding that the differences existing between the two were insubstantial. In reaching this conclusion, the court performed a function-way-result analysis. The court identified the "function" of edetate as "retard[ing] microbial growth in propofol oil-in-water emulsions." Nov. 2, 2005 Opinion, slip op. at 18. The court then defined the "way" that edetate worked as by metal ion chelation and found that the result achieved was "retard[ing] microbial growth to the extent required by the microbiological test set forth in the claims." Id., slip op. at 19. Based on the

[7] EDTA and DTPA belong to a broad class of structurally analogous compounds known as polyaminocarboxylic acids. Nov. 2, 2005 Opinion, slip op. at 13. Compounds belonging to this group have several amino groups and several acetic acid or carboxylic acid (COOH) groups.

evidence of record, the court found that calcium trisodium DTPA similarly retards microbial growth in an oil-in-water emulsion by metal ion chelation to retard the growth of the microorganisms to the extent required by the test set forth in the claims.

Mayne asserts that the district court clearly erred in defining the "way" as metal ion chelation.[8] Mayne contends that the proper definition of "way" is a narrower one, i.e., one that incorporates the specific metal ions that are chelated, the strength of the bonds that are formed during chelation, and the stability constants. Because Abraxis did not proffer evidence at trial that established those additional factors, Mayne argues that the "way" prong of the three-pronged test was unsupported by substantial evidence.

We disagree. "What constitutes equivalency must be determined against the context of the patent, the prior art, and the particular circumstances of the case." Graver Tank, 339 U.S. at 609. As the Supreme Court instructed, "[e]quivalence, in the patent law, is not the prisoner of a formula and is not an absolute to be considered in a vacuum." Id. Here, the district court properly assessed the "way" edetate works by referring to the patent and the evidence presented at trial. The record evidence supports the conclusion that the "way" in which both edetate and calcium trisodium DTPA perform as an antimicrobial agent is by metal ion chelation. Indeed, the patent specification describes edetates as "metal ion sequestering agent[s]." '520 patent, col.4 ll.33-35. Moreover, Mayne itself argued to the FDA that calcium trisodium DTPA is an

[8] Mayne also raises arguments on appeal concerning the function and result prongs of this test. Those arguments, however, are not properly before the court because Mayne failed to raise them below. Indeed, Mayne conceded that the dispute with respect to the doctrine of equivalents was limited to the "way" prong of the analysis. See J.A. at A1204 ("We agree, function and result aren't the issue here [with respect to the Graver Tank analysis]. Calcium trisodium [p]entetate is antimicrobial and it does achieve the result of killing those four microbes."). As such, those arguments are deemed waived and will not be addressed on appeal.

effective antimicrobial agent in its generic propofol formulation because "of its ability to chelate divalent metal ions." J.A. at A1907.

The court made fact-findings that calcium trisodium DTPA also inhibited microbial growth by chelating metal ions. In reaching this conclusion, the court credited the testimony of several experts at trial including Dr. Weiner, Dr. Tierno, and Dr. Knapp, all of whom testified about metal ion chelation and the use of calcium trisodium DTPA as a metal ion chelator to inhibit microbial growth. Additionally, the court relied on an expert report by Dr. Kille that was included in Mayne's FDA submission. The Kille report explained that calcium trisodium DTPA is effective as an antimicrobial agent "as a result of its ability to chelate divalent metal ions that are essential for many biological processes." J.A. at A1907. We thus conclude that the district court did not clearly err in defining "way" as metal ion chelation and in finding that that is the "way" in which calcium trisodium DTPA functions as an antimicrobial agent.

Secondly, we reject Mayne's argument that, as a matter of law, it is impermissible for the meaning of edetate to extend to other polyaminocarboxylates by equivalence. Mayne contends that by claiming their invention narrowly, i.e., by limiting the claim to edetate, Abraxis is barred from capturing DTPA, or any other polyaminocarboxylate, as an equivalent. Mayne cites Tanabe Seiyaku Co. v. United States International Trade Commission, 109 F.3d 726 (Fed. Cir. 1997) in support of this argument. In Tanabe, we affirmed the International Trade Commission's ruling of noninfringement under the doctrine of equivalents. The patent, which covered a method for preparing a pharmaceutical composition used for the treatment of various cardiovascular diseases, claimed, inter alia, five specific base-solvent combinations.

One claimed combination was potassium carbonate and acetone. Id. at 729. The accused product used a potassium carbonate and butanone combination, instead of acetone. We found that replacing acetone with butanone, a structurally similar compound, was a substantial change and thus not equivalent.

In reaching that conclusion, we noted that the inventor chose to specifically define his invention in the claims, the specification, and prosecution history in terms of the five base-solvent combinations. We noted that a person of skill in the art would know that the inventor could have claimed a broader term such as "ketone," which would have encompassed butanone, but decided to limit the claims to acetone. We further noted that the inventor distinguished his invention over prior art while prosecuting its foreign counterparts by arguing that the five base-solvent combinations yielded unexpectedly good results. Therefore, by describing the invention in that "sharply restricted nature" and by making arguments during prosecution that emphasized the importance of the five particular base-solvent combinations, we found that the inventor effectively disclaimed subject matter beyond the five combinations. Id. at 732. Thus, a competitor reading the patent and file wrapper would reasonably believe that butanone was not part of the invention.

That is not the situation here. Contrary to Mayne's assertion, the inventors did not clearly disavow other polyaminocarboxylates, including DTPA, by claiming edetate. There is no evidence that the patentees made a clear and unmistakable surrender of other polyaminocarboxylates, or calcium trisodium DTPA in particular, during prosecution. See Cordis Corp. v. Medtronic AVE, Inc., 339 F.3d 1352, 1363 (Fed. Cir. 2003) (noting that a "clear and unmistakable surrender of subject matter" is required to

find estoppel by argument). Indeed, the district court found that "the antimicrobial activity of calcium trisodium DTPA was unforeseeable during prosecution." Nov. 2, 2005 Opinion, slip op. at 37-38. Mayne itself acknowledged the unforeseeability of DTPA while prosecuting its own patent. Id. at 38. Thus, a person of ordinary skill in the art reading the patent would not conclude that by claiming "edetate," the patentees surrendered or waived coverage of all polyaminocarboxylates, including DTPA, as an equivalent, particularly in light of the unforeseeability of calcium trisodium DTPA as an equivalent. See Warner-Jenkinson, 520 U.S. 17, 37 (1997) (rejecting petitioner's argument that equivalents should be limited to known equivalents at the time of patent issuance, and not extend to after-arising equivalents); see also Kinzenbaw v. Deere & Co., 741 F.2d 383, 389 (Fed. Cir. 1984) ("[t]he doctrine of equivalents is designed to protect inventors from unscrupulous copyists and unanticipated equivalents") (citing Graver Tank, 340 U.S. at 607) (emphasis added). We thus reject Mayne's contention that, as a matter of law, the district court erred by determining that calcium trisodium DTPA is an equivalent of edetate.

Lastly, we reject Mayne's argument that the lack of known interchangeability between edetate and DTPA as an antimicrobial agent mandates the conclusion that the accused product does not infringe under the doctrine of equivalents. Mayne's theory is largely premised on the fact that Mayne was able to receive a patent on its generic propofol formulation. In fact, the absence of known interchangeability underscores that the patent applicant had no reason to foresee and claim DTPA in this combination. As stated in Warner-Jenkinson, known interchangeability is only one factor to consider in a doctrine of equivalents analysis. It aids the fact-finder in assessing the similarities and

differences between a claimed and an accused element. Warner-Jenkinson, 520 U.S. at 37 ("[a] skilled practitioner's knowledge of the interchangeability between claimed and accused elements . . . tells the fact-finder about the similarities or differences between those elements"). As discussed above, the court made factual findings that insubstantial differences exist between calcium trisodium DTPA and edetate, and further found that the separate patentability of Mayne's generic formula did "not outweigh the substantial evidence of equivalence between Mayne's calcium trisodium DTPA and the claimed edetate." Nov. 2, 2005 Opinion, slip op. at 39. We see no clear error in that finding.

In sum, we conclude that the district court's conclusion that Mayne's generic propofol formulation infringes the patents in suit under the doctrine of equivalents was not clearly erroneous. The court correctly determined that calcium trisodium DTPA performs substantially the same function in substantially the same way to achieve the same result as edetate. Indeed, that conclusion is consistent with the findings made by the district court that calcium trisodium DTPA was specifically chosen for the generic propofol formulation because of its structural similarities to edetate and the likelihood that it would match the product characteristics and stability profile of Abraxis' improved DIPRIVAN® formulation. Thus, Mayne fails to demonstrate that that finding amounted to clear error.

We have considered Mayne's remaining arguments and find them unpersuasive. Moreover, in light of our conclusion, we need not address Mayne's arguments with respect to the claims requiring disodium edetate. Accordingly, the court's judgment of infringement on this basis is affirmed.

CONCLUSION

For the foregoing reasons, we reverse the district court's claim construction as to the term "edetate" and the court's finding of literal infringement. The district court's finding of infringement under the doctrine of equivalents, however, is affirmed.

AFFIRMED.