IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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| **Fresenius Kabi USA, LLC,**<br><br>Plaintiff,<br><br>v.<br><br>**Dr. Reddy's Laboratories, Ltd.** and **Dr. Reddy's Laboratories, Inc.,**<br><br>Defendants. | Civil Action No. 13-925-RGA |
| **Fresenius Kabi USA, LLC,**<br><br>Plaintiff,<br><br>v.<br><br>**Watson Laboratories, Inc.** and **Actavis, Inc.,**<br><br>Defendants. | Civil Action No. 13-1015-RGA |

TRIAL OPINION

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August 25, 2014

Richard G. Andrews

ANDREWS, U.S. District Judge:

Plaintiff, Fresenius Kabi USA, LLC, brought this suit against Dr. Reddy's Laboratories, Ltd., Dr. Reddy's Laboratories, Inc. (collectively "Dr. Reddy"), Watson Laboratories, Inc., and Actavis, Inc. (collectively "Watson"), for infringement of four U.S. Patents: Nos. 5,714,520 ("the '520 patent"), 5,731,355 ("the '355 patent), 5,731,356 ("the '356 patent") and 5,908,869 ("the '869 patent") (collectively, "the patents in suit"). Fresenius sells a propofol injectable emulsion product, under the trade name Diprivan, and listed the patents in suit in the Food and Drug Administration's "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly referred to as the "Orange Book") as covering Diprivan. Defendants' Abbreviated New Drug Applications ("ANDAs") seek approval to engage in the commercial manufacture, importation, use, or sale of a propofol injectable emulsion product before the expiration of the patents in suit.

Fresenius asserts that the Defendants' generic products would infringe claims 1, 16, 36, and 37 of each of the patents in suit. The patents in suit all concern pharmaceutical compositions containing propofol and edetate. All asserted claims contain "edetate" as a limitation. The Court has adopted the construction of "edetate," set forth in *Abraxis Bioscience, Inc. v. Mayne Pharma (USA), Inc.*, 467 F.3d 1370, 1378 (Fed. Cir. 2006), as "EDTA and derivatives of EDTA, such as salts, but not including structural analogs." Fresenius concedes that Defendants' ANDA products do not literally infringe the "edetate" limitation. In order to expedite trial, the parties stipulated that the only issue for trial was whether Defendants infringe the "edetate" limitation under the doctrine of equivalents. (D.I. 21 in 13-925). The Court held a two day bench trial on June 2-3, 2014. As explained below, Fresenius did not prove infringement by a preponderance of the evidence.

## I. INFRINGEMENT

Because prior propofol emulsion formulations were susceptible to microbial contamination and growth, the formulations required the addition of an antimicrobial. The specification[1] makes clear that the critical part of the invention was the discovery that edetate is a broad-spectrum antimicrobial that can be added to propofol emulsions. '520 patent at Col. 4:22-37. The inventors studied at least ten known preservatives besides edetate. None of the others met the inventor's requirements. '520 patent at Col. 4:22-37.

The inventors explained that there were numerous difficulties in finding a preservative that could be added to the propofol emulsion. Specifically, the inventors had to find a hydrophilic additive, because it was believed that the antimicrobial properties were exerted in the aqueous phase. '520 patent at Col. 3:55-60. The inventors believed that a lipophilic preservative would not be effective because there would be insufficient amounts in the aqueous phase and too much in the lipid layer, leading to toxicity problems. '520 patent at Col. 3:60-67. During the inventors' investigation they considered or tested phenylmercuric acetate, phenylmercuric nitrate, benzyl alcohol, chlorobutanol, chlorocresol, phenol, sodium metabisulphite, sodium sulphite, sodium methyl hydroxybenzoate and sodium propyl hydroxybenzoate. '520 patent at Col. 4:22-28.

The inventors' discovery that edetate could be added to propofol as an antimicrobial resulted in the issuance of the patents in suit. The following claims of the '520 patent are representative:

> 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*

[1] The patents in suit all share a common specification.

> ATCC 6438, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027 and *Candida albicans* ATCC 10231 for at least 24 hours as measured by a test wherein a washed suspension of each said organism is added to a separate aliquot of said composition at approximately 50 colony forming units per ml. at a temperature in the range 20°-25° C., whereafter said aliquots are incubated at 20°-25° C. and are tested for viable counts of said organism after 24 hours, said amount of edetate being no more than 0.1% by weight of said composition.
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> 16. 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 wherein the amount of edetate is a molar concentration in the range $3x10^{-5}$ to $9x10^{-4}$.

'520 patent claims 1 and 16.

Defendants' ANDA products are oil-in-water emulsions. PTX-013; PTX-021; Tr. at 241:9-242:7. Propofol is dissolved in soybean oil along with egg phospholipids, which is then mixed with an aqueous solution. Tr. at 270:20-28, 280:11-24; PTX-013; PTX-021. After homogenization, the egg phospholipids act as emulsifiers, allowing the oil phase to be evenly distributed in tiny droplets throughout the continuous aqueous phase. Tr. at 247:21-249:7, 252:22-253:10, 259:20-260:4. Excess phospholipids combine to form spherical bilayer phospholipid structures, or liposomes. Tr. at 257:21-258:18.

Defendants certified that the only differences between Diprivan and Defendants' ANDA products are the antimicrobial agents. PTX-013; PTX-021. Dr. Reddy's formulation employs benzyl alcohol as the antimicrobial agent (PTX-013), while Watson employs sodium benzoate as the antimicrobial agent. (PTX-021). Fresenius concedes that there is no literal infringement, but claims that Defendants' ANDA products infringe under the doctrine of equivalents.

Fresenius does not allege that benzyl alcohol or sodium benzoate are equivalents of edetate.[2] Instead, Fresenius argues that benzyl alcohol and sodium benzoate do not actually work

[2] Since the inventors tested benzyl alcohol as an antimicrobial and found that it did not work, it clearly could not be claimed as an equivalent. *See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1322 (Fed. Cir.

as preservatives, and that it is dipropofol that is the true preservative in the formulations. The ANDAs do not identify dipropofol as a preservative, but as a possible degradation product of propofol, present at less than 0.005 mg/ml. Tr. at 531:7-19, 424:14-21, 425:3-8; DTX-236 at 4; DTX-026 at 20. Defendants' ANDA products have been tested for the presence of dipropofol, but none was detected within the accuracy of the test. DDX-91 at DRLPROP 00273; Tr. at 425:9-13, 531:23-532:5; DTX-247 at 1-3. In other words, while the testing did not show the presence of any dipropofol, it also did not prove that there was no dipropofol at all.

**A. Legal Standard**

The application of a patent claim to an accused product is a fact-specific inquiry. *See Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1332 (Fed. Cir. 2001). Literal infringement is present only when each and every element set forth in the patent claims is found in the accused product. *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575–76 (Fed. Cir. 1995). The patent owner has the burden of proving infringement by a preponderance of the evidence. *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984) (citing *Hughes Aircraft Co. v. United States*, 717 F.2d 1351, 1361 (Fed. Cir. 1983)). "Under [35 U.S.C.] § 271(e)(2)(A), a court must determine whether, if the drug were approved based upon the ANDA, the manufacture, use, or sale of that drug would infringe the patent in the conventional sense." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997).

Where there is no literal infringement, as here, there may still be infringement under the doctrine of equivalents. "The doctrine of equivalents allows the patentee to claim those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki*

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2009) ("Ensnarement bars a patentee from asserting a scope of equivalency that would encompass, or 'ensnare,' the prior art.") (internal citation omitted).

*Co.*, 535 U.S. 722, 733 (2002). A patentee may prove infringement under the doctrine of equivalents "by showing on a limitation by limitation basis that the accused product performs substantially the same function in substantially the same way with substantially the same result as each claim limitation of the patented product." *Crown Packaging Tech., Inc. v. Rexam Beverage Can Co.*, 559 F.3d 1308, 1312 (Fed. Cir. 2009).

Statements by applicants that characterize the unexpected properties of the invention, distinguish the prior art, and identify critical attributes of the invention give rise to argument based estoppel and may limit the scope of available equivalents. *See, e.g., PODS, Inc. v. Porta Stor, Inc.*, 484 F.3d 1359, 1368 (Fed. Cir. 2007); *Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1314 (Fed. Cir. 2001); *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1252 (Fed. Cir. 2000); *Pharmacia & Upjohn Co., v. Mylan Pharms., Inc.*, 170 F.3d 1373, 1378-79 & n.3 (Fed. Cir. 1999). Additionally, the scope of available equivalents may not encompass, or "ensnare," the prior art. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1323 (Fed. Cir. 2009) ("[T]here can be no infringement if the asserted scope of equivalency of what is literally claimed would encompass the prior art.") (internal citation omitted); *Wilson Sporting Goods Co. v. David Geoffrey & Assoc.*, 904 F.2d 677, 683 (Fed. Cir. 1990), *overruled in part on other grounds, Cardinal Chem. Co. v. Morton Int'l, Inc.*, 508 U.S. 83 (1993).

**B. Findings of Fact**

1. Benzyl alcohol is a well known preservative.
2. Sodium benzoate is a well known preservative.
3. Benzyl alcohol shows optimal activity at a pH below 5.
4. Sodium benzoate is known to be inactive in alkaline conditions.

5. Benzyl alcohol and sodium benzoate need not demonstrate optimal antimicrobial activity in order to meet the ANDA specifications.
6. Benzyl alcohol acts as an antimicrobial in Dr. Reddy's ANDA product.
7. Sodium benzoate acts as an antimicrobial in Watson's ANDA product.
8. Defendants' ANDA products were never tested for the presence of dipropofol.
9. Dipropofol is a phenol.
10. Dipropofol is lipophilic.
11. Edetate is a polyamino carboxylate.
12. Edetate is hydrophilic.
13. Edetate acts via metal ion chelation.
14. Edetate does not act via membrane insertion.
15. Dipropofol does not act via metal ion chelation.
16. Dipropofol does not act via membrane insertion.

**C. Conclusions of Law**

i. Dipropofol Is Not the Preservative in Defendants' ANDA Products

Fresenius has failed to prove that dipropofol is the preservative in Defendants' ANDA products. Both benzyl alcohol and sodium benzoate are well known preservatives. Tr. at 532:18-533:7; DDX-80; Tr. at 385:8-386:15; DTX-026 at 21; DTX-101 at 1. Fresenius theorizes that benzyl alcohol and sodium benzoate cannot work in Defendants' ANDA products because they are ineffective at the pH ranges present in the ANDA products. While this position has support in the literature, the testing shows that benzyl alcohol and sodium benzoate act as preservatives in Defendants' ANDA products.

Both Watson and Dr. Reddy's ANDA products were subjected to a preservative efficacy test ("PET"), which measures control of microbial growth over a period of 12 to 24 hours. Tr. at 534:11-535:20. In Dr. Reddy's product, the testing showed that formulations with higher levels of benzyl alcohol provided sufficient antimicrobial activity, whereas formulations with lower levels of benzyl alcohol did not. Tr. at 537:13-538:46; DDX-96 at DRLPROP 01034-37. Similarly, in Watson's product, the PET data confirms that sodium benzoate functions as a preservative. Tr. at 397:24-400:8; DTX-99 at 1; DTX-98 at 1; DTX-105 at 2, 5, 13, 17.

Dr. Reddy's ANDA product is specified to be released in a pH range of 7.0 to 8.5. PTX-017. Watson's ANDA product is specified to be released in a pH range of 7.5 to 8.5. PTX-21. Benzyl alcohol is known to have optimal activity at a pH below 5 and little activity above pH 8. PTX-125; Tr. at 75:15-21. Similarly, sodium benzoate's antimicrobial activity is attributable to the formation of undissociated benzoic acid, the presence of which is dependent on the pH. Tr. at 53:8-54:5, 459:23-460:14; PTX-124 at FRE-WAT000153; PTX-110 at FRE-WAT000066. Therefore, sodium benzoate is known to be ineffective under alkaline conditions. PTX-008; Tr. at 69:3-70:7.

Fresenius posits that the PET data does not reflect the activity of the identified preservatives because the literature states that the preservatives should not work at the pH levels present in the ANDA products. However, Dr. Maillard testified that sodium benzoate need not be extremely effective, but that it only had to prevent microorganisms from growing more than ten-fold after nine hours. Tr. at 387:2-389:1; DTX-060 at 6. Dr. Maillard explained that sodium benzoate could exert antimicrobial activity at higher pH levels, and that the Lambert paper showed antimicrobial activity of sodium benzoate at pH 8. Tr. at 289:7-391:25, 392:1-397:3; DTX-122; DTX-206; DTX-236 at 3.

Fresenius attacks Watson's PET testing because the results are not linear. (D.I. 82 in 13-925 at p. 8). Fresenius argues that because the testing shows a rather large variability, something other than the identified preservatives, *i.e.*, dipropofol, is providing the antimicrobial effect. I agree that the PET testing shows some variability. However, it unequivocally shows that sodium benzoate and benzyl alcohol are acting as preservatives, even if not at an optimal activity level.

Fresenius offered no evidence that samples of either product actually contain any amount of dipropofol. This fact alone, however, is not legally relevant, as, "when a drug manufacturer seeks FDA approval to market a generic compound within the scope of a valid patent, it is an infringement as a matter of law." *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271, 1280 (Fed. Cir. 2013); *see also Ferring B.V. v. Watson Labs., Inc. – Florida,* No. 2014-1416, slip op. at 13-14 (Fed. Cir. Aug. 22, 2014). However, the lack of testing weighs against Fresenius' equivalents argument. While Defendants are held to their ANDA specifications, Fresenius never offered any evidence that the ANDA products actually contained dipropofol. Fresenius could have tested the samples, but did not.[3]

Lastly, Fresenius does not offer any explanation as to why dipropofol would now act as an antimicrobial, but did not in the prior art. Presumably dipropofol was present in the prior art formulations to the same extent as it might be present in Defendants' ANDA products. If dipropofol was now acting as an antimicrobial, it should have acted as such in the prior art.

ii. Dipropofol Does Not Function in Substantially the Same Way as Edetate

[3] While Fresenius was not under an obligation to prove that the ANDA products contained dipropofol, it would have been probative of whether the identified preservatives were responsible for antimicrobial activity. Because the products were not shown to contain dipropofol, Fresenius' theory is less plausible. It is hard to prove the product works because of the presence of dipropofol when such testing as has been done does not reveal the presence of dipropofol.

Even assuming that dipropofol acts as an antimicrobial in Defendats' ANDA products, it is substantially different from edetate.[4] Dipropofol is a phenol whereas edetate is a polyaminocarboxylate. Tr. at 343:23-344:6; *Abraxis*, 467 F.3d at 1379 n.7. Dipropofol is highly lipophilic and will be concentrated in the oil phase. Tr. at 242:13-21, 243:5-11, 283:20-284:7, 294:12-24. Conversely, edetate is distributed throughout the aqueous phase. '520 patent at Col. 3:55-60.

Edetate's function is to retard microbial growth, and the result is the retarding of the microbial growth as set forth in the claims. Based on the stipulation, it is not contested that the ANDA compounds achieve the results set forth in the claims. The dispute here is over the "way" of the "function, way, result" test. D.I. 67 in 13-925 at Ex. B ¶¶ 23-29. Edetate acts via metal ion chelation. *Abraxis*, 467 F.3d at 1370. Fresenius now argues that edetate also acts via membrane insertion, and that dipropofol also acts in these two ways. I do not agree that edetate acts via membrane insertion. Furthermore, Fresenius did not prove that dipropofol acts via metal ion chelation or membrane insertion.

Fresenius cited to one reference to show that edetate acts via membrane insertion. PTX-080; Tr. at 135:12-18, 140:15-141:4. However, this reference, the Prachayasittikul paper, was performed on an artificial cellular membrane. Tr. at 502:15-22, 503:6-14. One cannot assume that edetate will insert into cell walls of actual microorganisms based upon its interaction with an artificial cellular membrane. Tr. at 412:14-416:13. One paper which observed membrane insertion in an artificial membrane is not enough to prove that edetate acts via membrane

[4] Edetate has been shown to be a powerful antimicrobial against gram-positive and gram-negative bacteria. Tr. at 406:16-407:9, 408:2-14. Dipropofol has been shown to have antimicrobial activity against gram-positive bacteria. PTX-077; PTX-079; Tr. at 118:8-120:5, 488:1-20. Testing has not proven whether dipropofol is active against gram-negative bacteria. Tr. 431:14-437:3, 543:2-13.

insertion in actual microorganisms, especially when the scientific community agrees that edetate acts via metal ion chelation.

Even if Fresenius had proved that edetate acts via membrane insertion as well as metal ion chelation, there was no convincing evidence that dipropofol also acts via these mechanisms. Dr. Hancock's unrebutted testimony was that dipropofol does not act via metal ion chelation. Chelation requires that the chelating agent bond using more than one donor atom. Tr. at 561:17-562:14. Dr. Hancock explained that dipropofol has two hydroxyl groups which are capable of binding weakly to a metal ion, but those groups are too far apart, and dipropofol is too rigid, to permit both hydroxyl groups to bind to a metal ion at the same time. Tr. at 565:2-566:17. Furthermore, Dr. Hancock tested dipropofol to determine its binding constant. He determined that "calcium was not able to form a complex with dipropofol at all." Tr. at 537:22-574:1. Assuming a margin of error, he then calculated dipropofol's binding constant as less than or equal to one. Tr. at 570:18-23. Dr. Hancock then compared this binding constant with those of EDTA and other edetate derivatives, and concluded that dipropofol would "not be able to bind calcium very strongly at all, and this would certainly be very far from sufficient to produce a bacteriocidal effect by binding a metal ion." Tr. at 573:15-581:21.

Fresenius' experts cited only a single reference for the proposition that dipropofol binds with iron ions. DTX-132; PTX-56; DDX-20. The reference claimed that dipropofol bound 61% of the iron ions in an experiment; however, Dr. Davis, Fresenius' own expert, forthrightly admitted that that calculation was incorrect. Tr. at 351:14-352:13. The reference made no claim that dipropofol's supposed binding of ions was strong enough to exert an antibacterial effect, nor did Fresenius' experts provide data to that effect. Tr. at 351:4-13. Therefore, I find that Fresenius did not prove by a preponderance of the evidence that dipropofol acts via metal ion chelation.

Fresenius did not prove that dipropofol acts via membrane insertion. In fact, the way dipropofol acts is entirely unproven. Fresenius offered no evidence that dipropofol acts via membrane insertion. Instead, Fresenius presented evidence that honokiol, a similar lipophilic dimeric phenol, might act via membrane insertion.[5] Tr. at 323:11-19, 324:1-5; PTX-061. Fresenius' expert, Dr. Davis, admitted that he would not expect all diphenols to have substantial antibacterial activity. Tr. at 342:9-343:13. In fact, Dr. Davis limited his testimony by testifying that because honokiol has antimicrobial activity, it "would *suggest* to me that dipropofol *could* have such activity." Tr. at 345:6-14 (emphasis added). Dr. Davis admitted that he was proposing these mechanisms "for the first time here in this Court without having done any testing of [his] own." Tr. at 334:12-15. Such proposals cannot form the basis for a finding of infringement.

Accordingly, I find that Fresenius has not proven that Defendants' products contain an equivalent of edetate. At some point, Defendants' ANDA products may contain dipropofol. Dipropofol, however, is not an equivalent of edetate. Edetate acts via membrane insertion. Dipropofol's mechanism is unknown. Therefore there can be no infringement under the doctrine of equivalents.

## II. CONCLUSION

Plaintiff has failed to prove that Defendants' ANDA products infringe claims 1, 16, 36, and 37 of the patents in suit. The Defendants should submit an agreed upon form of final judgment within two weeks. All pending motions are dismissed as moot.

[5] Defendants contest that honokiol acts via membrane insertion. I need not decide how honokiol acts to conclude that dipropofol has not been shown to act via membrane insertion.