IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

FRESENIUS KABI USA, LLC, Plaintiffs, v. DR. REDDY'S LABORATORIES INC. and DR. REDDY'S LABORATORIES LTD., Defendants.	Civil Action No. 13-cv-00925 (RGA) PUBLIC VERSION

FRESENIUS KABI USA, LLC, Plaintiffs, v. WATSON LABORATORIES, INC. and ACTAVIS, INC. Defendants.	Civil Action No. 13-cv-01015 (RGA) PUBLIC VERSION

DEFENDANTS' MEMORANDUM OF LAW IN SUPPORT OF THEIR MOTION TO LIMIT THE APPLICATION OF THE DOCTRINE OF EQUIVALENTS

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I. INTRODUCTION

Fresenius Kabi USA, LLC ("Fresenius") accuses defendants[1] of infringing claims 1, 16, 36 and 37 of four propofol-edetate combination patents. Only through clear and unequivocal argument, amendment, and disclaimers concerning the centrality of edetate did applicants obtain allowance of the claims. The patents state their inventors "unexpectedly found that edetate, which was not regarded as a broad spectrum antimicrobial agent was ***the only agent*** that would meet our requirements." Shelhoff Decl., Ex. 1, '520 patent, 4:30-33[2] (emphasis added). The prosecution history cites this portion of the specification twice and repeatedly echoes its conclusion – that edetate with propofol was special and unique because only edetate inhibited the growth of both gram-negative and gram-positive bacteria. The estoppel arising from these arguments, amendments and disclaimers at least encompasses the accused products here.

Defendants relied upon the representations in the patents and their prosecution histories to design around these patents. Thus, defendants' proposed generic propofol products include no edetate, nor anything related to it. DRL [redacted]

[1] "defendants" collectively refers to Dr. Reddy Labs., Inc. and Dr. Reddy's Labs., Ltd. ("DRL") and Watson Labs., Inc. and Actavis, Inc. ("Watson").

[2] The four patents in suit, U.S. Patent Nos: 5,714,520 (the "520 patent"); 5,731,355; 5,731,356; and 5,908,869 are annexed as exhibits 1-4 of the Shelhoff Decl. All subsequent citations to a portion of a patent specification refer to the '520 patent (exhibit 1), and reference that portion by column and line numbers (as here referring to column 4, lines 30-33). Because the other patents in suit issued from respective divisional applications derived from the application that led to the '520 patent, the specifications of all four patents in suit are essentially the same. Thus, every citation to the '520 patent here also applies to the other three patents in suit, though corresponding column and/or line numbers may differ.

Having conceded that defendants' products have no edetate, Fresenius retreats to a doctrine of equivalents theory that defendants' products may in the future contain an unspecified amount of "dipropofol." Fresenius now supposes that dipropofol (1) is present in defendants' products; (2) is responsible for preserving defendants' products; and (3) works in the same way and achieves the same result as does edetate in the claimed formulations.[3]

As a matter of law, however, Fresenius is estopped from asserting that a substance lacking broad spectrum antimicrobial effect against both gram-negative and gram-positive bacteria is somehow equivalent to edetate. During prosecution, the inventors argued repeatedly and successfully for patentability over the prior art because they said edetate unexpectedly retarded growth of both gram-negative and gram-positive bacteria. They insisted that such broad spectrum effectiveness was "critical" to the invention. Accordingly, prosecution history estoppel precludes Fresenius from contending that dipropofol, a component that indisputably lacks an antimicrobial effect against both gram-negative and gram-positive bacteria, is equivalent to edetate.

II. STATEMENT OF FACTS

A. Defendants' Products Do Not Contain Dipropofol or Edetate.

There is no evidence that dipropofol is present in any of the defendants' products. The dipropofol discussed in the few articles relied on by Fresenius was made artificially by chemical synthesis, and was not the result of the degradation in any propofol emulsion. Of course, the sole reason Fresenius' has focused on dipropofol is because defendants' products have no edetate.

[3] The Court should apply the Federal Circuit's ruling as to what the "function," "way" and "result" of edetate is in these patents. *See Abraxis Bioscience v. Mayne Pharma (USA) Inc.*, 467 F.3d 1370 (Fed. Cir. 2006). Specifically, Fresenius must prove that dipropofol performs an antimicrobial function in substantially the same "way" as the chemical process known as "ion chelation," and achieves the same "result" of "retard[ing] microbial growth to the extent required by the microbiological test set forth in the claims." *Id.* at 1379-1381 (Fed. Cir. 2006).

B. The Patents in Suit Teach that Edetate Is Essential.

The patents in suit focus on "edetate." The '520 patent is titled "Propofol Composition Containing Edetate." The remaining patents in suit share this same title or are titled "Pharmaceutical Compositions of Propofol and Edetate." The specification uses the word "edetate" 60 times. The abstract describes the invention as "containing a[n] amount of edetate sufficient to prevent significant growth of microorganisms for at least 24 hours." The specification explains that "the present invention . . . comprises an amount of edetate sufficient to prevent significant growth of microorganisms for at least 24 hours," that only edetate provides "advantages," and further lauds disodium edetate as "exceptional." *Id.*, 4:57-67, 4:66. The inclusion of edetate that "prevent[s] significant growth of microorganisms for at least 24 hours" is characterized as "critical." *Id.*, 4:58.

Claim 1 of the '520 patent reads:

> 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 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.

The claims make clear that the role of edetate in the claimed formulations is to control growth of both gram-positive bacteria (*Staphylococcus aureus*) and gram-negative bacteria

(*Psudomonas aeruginosa* and *Escherichia coli*).[4] The patent specifications never suggest the possibility of using any preservative other than edetate. The only other preservatives discussed are those that did *not* work.

> **After significant effort including consideration of the known preservatives** phenylmercuric acetate, phenylmercuric nitrate, benzyl alcohol, chlorobutanol, chlorocresol and phenol and the study of the known preservatives sodium metabisulphite, sodium sulphite, sodium methyl hydroxybenzoate and sodium propyl hydroxybenzoate, **we were unable to find a preservative that met our requirements**. 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.**

'520 Patent, 4:22 - 37 (Emphasis added).

C. Prosecution History Limits Equivalents for Edetate.

1. Applicants Stressed that Edetate Was Critical.

During prosecution, applicants argued that only edetate met their "critical objective," which was "to find an antibacterial agent that would be effective, at reasonably low concentrations, against both Gram-positive bacteria (such as *Staphylococcus aureus*) and Gram-negative bacteria such as *Escherichia coli*)." October 15, 1996 Amendment and Response (PH 105 - 119).[5]

2. Applicants Argued that Edetate Produced Unexpected Results.

A legion of "unexpected result" claims for edetate's antibacterial action against gram-positive and gram-negative bacteria appear in the prosecution history:

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[4] The claims likewise make clear that edetate must also control growth of *Candida albicans*, which is not a bacterium, but a yeast. Thus any equivalent to edetate must also control growth of *Candida albicans*.

[5] The prosecution history of the '520 patent is annexed as Ex. 5 to the Shelhoff Declaration and is sequentially labeled with page numbers with the prefix "PH" (for prosecution history). This and subsequent references here to "PH" numbers refer to Ex. 5 to the Shelhoff Declaration.

a. "This art [Russell-2], when considered as a whole, strongly suggests that edetate would not function to meet the objective of the present invention for broad spectrum antibacterial coverage against both Gram-positive and Gram-negative bacteria commonly encountered in hospital environments." PH 150.

b. "A number of possible additives were studied (*See, e.g.*, specification at page 6, lines 18-30).[6] Some caused instability of the emulsion; others failed to provide the level and spectrum of antimicrobial activity that was being sought. Eventually, it was unexpectedly found that edetate provided an appropriate balance of these competing requirements. Comparative data on the antimicrobial effectiveness of some of these agents is provided in the specification at pages 16-18." PH 112.

c. "[T]here is no disclosure in Hart of any beneficial effects of EDTA alone on Gram-positive bacteria. To the contrary, the skilled person reading Hart would be led to believe that EDTA would not provide the broad spectrum of coverage required by the invention of both Gram-positive and Gram-negative bacterial infection. In particular, Hart would lead the skilled person to believe that EDTA would not be effective against the most prevalent *Staphylococcus aureus* (Gram-positive) infection reported in the MMWR and New England Journal of Medicine references discussed in the background." PH 116-117 (emphasis in original).

d. "Chew concludes in its abstract that edetate at a concentration of 250 ppm has a bactericidal effectiveness against Gram-positive bacteria, and that it is "much less effective against gram-negatives." Chew thus points in an opposite direction from Hart, and would lead to confusion as to the relative effectiveness of edetate.

It is also highly significant that that Chew reports that edetate is relatively ineffective against E. coli…" PH 117 (emphasis in original).

e. "[W]hen the art is considered as a whole (as it must be), it strongly suggests that edetate would not function to meet the objective of the present invention for broad spectrum antibacterial coverage against both Gram-positive and Gram-negative bacteria commonly encountered in hospital environments. Thus, there was no motivation for persons skilled in the art to select edetate from the antimicrobial art of record, and to combine it with the known propofol oil-in-water emulsion compositions, to achieve the compositions as presently claimed." PH 118 (emphasis in original).

f. "Once having made the decision to investigate antimicrobial agents, edetate was by no means a clear choice to fill applicants' combination of objectives, particularly the need for broad spectrum coverage at a relatively low concentration." PH 149.

[6] This citation corresponds to the published specification of the '520 patent, 4:22-37, which is the same paragraph quoted on the top of page 4 of this brief.

3. Applicants Distinguished Prior Art by Relying on Edetate.

Applicants argued that including edetate distinguished their invention over prior art.

a. "This art [Russell-2], when considered as a whole, strongly suggests that edetate would not function to meet the objective of the present invention for broad spectrum antibacterial coverage against both Gram-positive and Gram-negative bacteria commonly encountered in hospital environments." PH 150.

b. "[T]here is no disclosure in Hart of any beneficial effects of EDTA alone on Gram-positive bacteria." PH 116;

c. "Chew thus points in an opposite direction from Hart, and would lead to confusion as to the relative effectiveness of edetate. It is also highly significant that that Chew reports that edetate is relatively ineffective against E.coli…" PH 117;

d. "Nakamura et al. adds nothing further to the above discussion of Glen, Hart and Chew that would motivate persons skilled in the art to make the propofol oil-in-water emulsions containing edetate of the type presently claimed." PH 119.

III. ARGUMENT

A. Fresenius May Not Assert that Compounds Lacking Gram-Positive and Gram-Negative Antibacterial Function Are Equivalents for Edetate.

1. Fresenius May Not Vitiate the Edetate Elements in its Claims.

The "all elements rule" prevents the doctrine of equivalents from being applied where it would vitiate a claim limitation. *Warner-Jenkinson Co. v. Hilton Davis Chemical Co.*, 520 U.S. 17, 29 (1997). The Federal Circuit, in applying this rule, has affirmed summary judgment of no infringement where the limitation at issue concerned bacteria *E. coli*," but where the patentee argued equivalency of an entirely different bacteria. *Thermus aquaticus*. *Carnegie Mellon University v. Hoffmann-LaRoche Inc.*, 541 F.3d 1115, 1128-29 (Fed. Cir. 2008).

More recently, Judge Robinson of the District of Delaware held that asserting an enzyme (from *L. grayi*) to be the equivalent of an entirely different enzyme (from *L. lactis*) violated the all elements rule. *Gevo, Inc. v. Butamax Advanced Biofuels LLC*, No. 13-576-SLR, 2013 WL 3914467 at *11 (D. Del. July 26, 2013). Because the two enzymes came from different sources

and had different structures, Judge Robinson reasoned that construing "[the claimed enzyme from *L. grayi*] to mean 'any enzyme' would read [or vitiate] the limitation out of the patent." *Id.*

Here, as in *Gevo*, the alleged equivalent dipropofol is utterly unrelated to the claimed compound edetate. It is undisputed that they share no structural similarity, and no chemical or biological family or kinship. To allow dipropofol to be an equivalent of edetate would be to allow an unbounded universe of substances unrelated to edetate to infringe, thereby reading out "edetate" from the claims. Applicants could have broadly claimed a propofol emulsion with increased resistance to bacterial contamination. Instead they claimed "edetate" specifically and attributed to it properties that they insisted were unexpected, unique, and "critical." Fresenius may not now claim that any other substance with any anti-microbial effect infringes their claims.

Applicants repeatedly argued edetate was critical to the invention and unique in its ability over all other known preservatives to retard the growth of both gram-negative and gram-positive bacteria. For instance, applicants insisted that only edetate met their "critical objective… to find an antibacterial agent that would be effective, at reasonably low concentrations, against both Gram-positive bacteria (such as *Staphylococcus aureus*) and Gram-negative bacteria (such as *Escherichia coli*)." PH 105 – 119.

Fresenius is estopped from asserting any equivalent of edetate, and in particular from asserting an equivalent that lacks antimicrobial effect against both Gram-negative and Gram-positive bacteria, in light of the inventors' repeated insistence that: (1) edetate in the invention produced the unexpected result of broad spectrum efficacy, against both Gram-negative and Gram-positive bacteria; (2) the unexpected broad spectrum effect of edetate was "critical" to the invention; and (3) the invention was patentable over prior art known antimicrobials because of that "critical" broad spectrum antimicrobial effect. *See also*, n. 4, above. The public is entitled to

rely (as defendants did) on what the applicants themselves say makes their inventions patentable over prior art – in this case, the unexpected result that edetate has antimicrobial effect against both gram-positive and gram-negative type bacteria.

2. Argument-Based Estoppel Limits the Scope of Permissible Equivalents for "Edetate."

Argument-based prosecution history estoppel arises from the applicants' statements (recounted in §II(C) above), because they are a clear and unmistakable surrender of the use of alternative preservatives, and most certainly alternative preservatives that have no antimicrobial activity against both gram-positive and gram-negative bacteria. *See e.g., Pods, Inc. v. Porta Stor, Inc.,* 484 F.3d 1359, 1368 (Fed. Cir. 2007).

Through its arguments[7] to the PTO during the prosecution of the patents in suit, applicants argued that: (1) the use of edetate was critical to achieve broad spectrum antimicrobial activity against both gram positive and gram negative bacteria; (2) the incorporation of edetate into the formulation unexpectedly produced superior results; (3) the absence of edetate led to bad results; and (4) their invention could be distinguished from the prior art because they chose edetate in particular as their anti-microbial additive. Thus, as explained below, all four markers of prosecution history estoppel are here.

[7] Also, amendment-based estoppel applies to "said amount of edetate being no more than 0.1% by weight of said composition," which applicants added to narrow their claims overcome a prior art rejection. PH 131-133. Applicants distinguished their invention over prior art because the prior art used more edetate than the invention, and used edetate only against gram negative bacteria, whereas edetate in the invention worked against both gram positive and negative bacteria. PH 128. This amendment creates an estoppel. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 740-741 (U.S. 2002); *Honeywell Int'l v. Hamilton Sundstrand Corp.*, 370 F.3d 1131, 1141 (Fed. Cir. 2004). As in *Glaxo Wellcome, Inc. v. Impax Labs, Inc*., 356 F.3d 1348, 1357 (Fed. Cir. 2004), this estoppel applies to unamended claims with the "critical" element.

First, affirmative statements about the superiority and inventive nature of particular subject matter can lead to a finding of prosecution history estoppel. *See e.g., Bayer AG v. Elan Pharm. Research Corp.,* 212 F.3d 1241, 1252 (Fed. Cir. 2000) (citing Bayer's "affirmative statements" about the "superiority" of its "inventive range"); *Pharmacia & Upjohn Co., v. Mylan Pharm., Inc.*, 170 F.3d 1373, 1378-79 & n.3 (Fed. Cir. 1999) (spray-dried lactose was "an indispensable component of the claimed formulations" and was "crucial" to the success of the formulations); *Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1314 (Fed. Cir. 2001) (finding estoppel from applicants' arguments that "only" a particular material had a desired property). As discussed above (§ II(C)(1)), applicants here similarly emphasized the criticality of edetate, and literally used the word "critical" in doing so.

Second, a claim of unexpected results can lead to an estoppel. In *Bayer*, the Federal Circuit determined that a Bayer, repeatedly argued that its claimed range of 1.0 to 4 m^2/g produced unique results and was a superior and inventive range and thus Bayer had surrendered micronized nifedipine beyond the upper limit of 4 m^2/g set forth in the patent. *Id.* at 1252-53. The patentee's emphasis on the inventive nature of the claimed range and the disadvantages of material outside the claimed range amounted to a clear and unmistakable surrender. *Id.* at 1254. Similarly, a patentee's emphasis on "opposite-side gating" gave up any argument that same-side gating was equivalent to opposite-side gating. *Tex. Instruments v. ITC,* 988 F.2d 1165, 1175 (Fed. Cir. 1993). Fresenius made parallel arguments regarding edetate. *See* (§ II(C)(2)) above.

A third signpost of prosecution history estoppel is an applicant's argument that disadvantages arise from the absence of the claimed inventive feature – in effect, a representation of what the invention is *not*. *See e.g., Pharmacia*, 170 F.3d at 1378 (finding that first paragraph of response to an office action was "reasonably interpreted as a broad disclaimer of what the

invention was not"); *Tex. Instruments*, 988 F.2d at 1174 ("The prosecution history. . . shows that the inventors placed special emphasis on locating the gate on the opposite side of the mold . . . because locating the gate on the same-side of the mold did not work."); *Isham v. Pillowtex Corp.*, 91 F. Supp. 2d 992, 998-99 (E.D. Tex. 2000) (patentee gave up coverage of mattress pad with stretchable skirt around the entire mattress by stating that this "total panel concept" was "unsuccessful" because it caused an unkempt appearance), *aff'd mem.*, 15 Fed. Appx. 800 (Fed. Cir. 2001). Here applicants' raised similar lamentations from omitting edetate. *See* § II(C)(3).

Fourth, applicants distinguished their invention over the prior art by pointing to the feature for which they now seek equivalents. *See Spine Solutions, Inc., v. Medtronic Sofamor Danek USA, Inc.*, 620 F.3d 1305, 1317 (Fed. Cir. 2009); *Colgate Palmolive Co., v. W.L. Gore & Assoc. Inc.*, 919 F. Supp. 767, 772-73 (D.N.J. 1996). If a patentee argues that inclusion of a particular feature is the difference between patentability and not, the patentee may not later argue that it is unfair to exclude from the reach of its claims an accused device that lacks this feature. *See* § II(C)(4)).

IV. CONCLUSION

For the foregoing reasons, defendants respectfully request that the Court grant their motion and find that prosecution history estoppel bars the application of the doctrine of equivalents to "edetate" and particularly with respect to compounds that do not have anti-bacterial action against both gram-positive and gram-negative bacteria.

Dated: April 18, 2014

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