IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALCON INC., ALCON VISION, LLC, and ALCON LABORATORIES, INC., *Plaintiffs*, v. PADAGIS ISRAEL PHARMACEUTICALS LTD., PADAGIS US LLC, and PADAGIS LLC, *Defendants*.	§ § § § § § § § § § § § §	Civil Action No. 22-1422-WCB **REDACTED - PUBLIC VERSION**

MEMORANDUM OPINION AND ORDER

In this Hatch-Waxman Act patent case, plaintiffs Alcon Inc., Alcon Vision, LLC, and Alcon Laboratories, Inc., (collectively, "Alcon") have asserted various claims of U.S. Patent Nos. 9,044,484 ("the '484 patent") and 9,421,265 ("the '265 patent") against defendants Padagis Israel Pharmaceuticals Ltd., Padagis US LLC, and Padagis LLC (collectively, "Padagis"). Specifically, Alcon alleges that the subject of Padagis's Abbreviated New Drug Application No. 204251 ("Padagis's ANDA product") infringes claims 1–3 and 6–23 of the '484 patent and claims 13–19 of the '265 patent.

Padagis moves for summary judgment of noninfringement of all asserted claims. For the reasons set forth in this opinion, summary judgment of no literal infringement is GRANTED for all asserted claims. Summary judgment of no infringement under the doctrine of equivalents is GRANTED as to Alcon's theories that sodium chloride, [redacted] are equivalent to mannitol, but DENIED with respect Alcon's theory that tartaric acid

is equivalent to mannitol. Alcon moves to exclude various opinions of Padagis's experts under *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993), and Fed. R. Evid. 702. Alcon's motion is DENIED.

I. BACKGROUND

Many pharmaceutical compositions are required to be sterile. Normally, sterility can be achieved through sterile manufacturing and packing or through the use of chemical preservatives. *See* '484 patent at col. 1, ll. 35–45. Sterile manufacturing, however, cannot prevent contamination after a product is opened. For that reason, multi-dose ophthalmic products, such as eye drops, must be kept sterile by using chemical preservatives. But chemical preservatives have their own drawbacks. Most notably, chemical preservatives tend to cause irritation to the eyes, which are "particularly sensitive to exogenous chemical agents." *See id.* at col. 1, line 66, through col. 2, line 8.

One of the ways in which toxicity from chemical preservatives is minimized is by using "borate-polyol complexes."[1] *See id.* at col. 2, ll. 51–62. When combined with traditional preservatives, borate-polyol complexes can increase antimicrobial efficacy without a corresponding increase in toxicity. However, borate-polyol complexes pose another problem. They are powerful buffers, meaning that they strongly resist changes to pH. Some level of buffering capacity is desirable to ensure that a pharmaceutical composition is kept close to the desired pH.[2] Too high a buffering capacity, however, can be problematic. When drugs that too

[1] Polyols are multi-carbon compounds with more than one alcohol (-OH) group. Some examples of polyols include mannitol, glycerin, xylitol, sorbitol, and polypropylene glycol. *See* '265 patent at col. 4, ll. 14–16.

[2] Buffering capacity is a quantitative measure of a solution's resistance to a change in pH.

strongly resist a change in pH are administered to the eyes, the eyes may tear up as they struggle to maintain their natural pH, resulting in discomfort to the user.

The inventors of the ’265 and ’484 patents sought to optimize ophthalmic pharmaceutical compositions by reducing the excessive buffering effect of borate-polyol complexes. The asserted patents are both directed to aqueous pharmaceutical compositions containing low concentrations of two different polyols. The patents share a substantially similar specification, which describes a composition whose principal features are a “first polyol,” a “second polyol,” and borate. The “first polyol” is preferably one whose borate-polyol complex significantly enhances the formulation’s resistance to a change in pH. *See* ’484 patent at col 4, ll. 57–60. The “second polyol” is one with anti-microbial features, but with weaker resistance to a change in pH than the first polyol *Id.* at col. 4, ll. 60–63. By adjusting the ratio between the first and second polyols, formulators can control the buffering capacity of the solution.

The patent also discloses formulations including only a single polyol. One of those formulations is “Composition S,” which is described in Table I of both patents. Composition S contains propylene glycol, which belongs to the “second polyol” group. Notably, however, it contains no mannitol. Padagis’s ANDA product is nearly identical to Composition S. The only differences between Padagis’s ANDA product and Composition S are that (1) the ANDA product calls for a 50 percent higher concentration of benzalkonium chloride (a preservative), and (2) the ANDA product includes active ingredients such as brimonidine tartrate, whereas Composition S has no active ingredient.

All the asserted claims are directed to a composition including the “first polyol” comprising either mannitol, sorbitol, or some combination thereof, with a specified minimum concentration.

Claim 13 of the ’265 patent is the broadest asserted claim with respect to the first polyol limitation. That claim recites:

> A multi-dose ophthalmic composition, comprising:
>
> *a first polyol, the first polyol being selected from mannitol, sorbitol or a combination thereof and wherein the concentration of the first polyol is at least 0.01 w/v % but no greater than 0.5 w/v %;*
>
> a second polyol, the second polyol being selected from propylene glycol, glycerine or a combination thereof wherein the second polyol is at least about 0.1 but less than about 5 w/v % of the composition;
>
> an effective amount of borate, the effective amount being less than about 0.5 w/v % of the overall composition;
>
> therapeutic agent;
>
> BAC as an anti-microbial preservative, the concentration of BAC in the composition being greater than 0.00001 w/v % but less than 0.0035 w/v %; and
>
> water;
>
> wherein the composition is substantially free of any preservatives other than benzalkonium chloride and wherein the composition is a suspension with the therapeutic agent and carboxyvinyl polymer as a suspending agent.

’256 patent at col. 19, ll. 16–36 (emphasis added). The other asserted claims are broader, at least with respect to the first polyol limitation. *See* ’484 patent at col. 17, ll. 6–7 (claiming a composition including a first polyol that is either mannitol, sorbitol, or a combination thereof, with a concentration between 0.15 and 0.5 w/v percent); *id.* at col. 17, ll. 59–60 (same); *id.* at col., 18, ll. 35–36 (claiming a composition including between 0.15 and 0.5 w/v mannitol).

Padagis’s ANDA product does not intentionally include mannitol or sorbitol. *See* Dkt. No. 185-1, Ex. 1 at PADBRI0002469 (listing ingredients). However, the manufacturer of Padagis’s ANDA product, [redacted], manufactures a different product in the same 300-liter tank that is used to manufacture the ANDA product. The manufacturing process for the other product,

[redacted]. After cleaning the tank between uses, Padagis measures the residual concentration of active ingredients in the tank, but not the concentrations of excipients. *See* Dkt. No. 185-1, Ex. 1 at PADBRI0002469 (cleaning validation report). Mannitol is an excipient, so potential cross-contamination from mannitol is not measured. The lowest claimed mannitol concentration, 0.01 w/v percent, could be achieved if 30 grams of mannitol were to cross-contaminate a 300-liter batch.

Alcon's expert, Dr. Steven Little, stated in a declaration that "the maximum amount of mannitol that is available for carry over would be [redacted]," which would mean that the composition in the tank would be [redacted] w/v percent mannitol. Dkt. No. 203 at ¶ 29. Put differently, Dr. Little represented that even after emptying and cleaning the tank, up to 100 percent of the mannitol used in Padagis's [redacted] might carry over into Padagis's ANDA product. In support of that proposition, Dr. Little noted that Padagis has not established any maximum tolerable amount of carryover mannitol. *Id.* at ¶ 31. Dr. Little further explained that FDA regulations allow up to 4 w/v percent mannitol before contamination becomes a safety concern. *See* Dkt. No. 203 at ¶ 30. Accordingly, Dr. Little stated that in his opinion Padagis's ANDA is not silent with respect to that limitation. Rather, he concluded that "[b]ecause Padagis's ANDA seeks to market [a product] that can contain a concentration of mannitol that encompasses [the] claimed ranges, Padagis's ANDA seeks FDA approval for an ANDA Product that meets the limitations of each" of the asserted claims. *Id.* at ¶ 32.

In his expert report, Dr. Little also stated that the "first polyol" limitation is met under the doctrine of equivalents. *See generally* Dkt. No. 185-2, Ex. 2 at ¶¶ 484–547. Dr. Little identified two sets of components that are purportedly equivalent to mannitol or sorbitol, the claimed polyols.

First, Dr. Little explained that mannitol is a tonicity agent, meaning that it functions to adjust the osmolality of the solution. Sodium chloride, which is an ingredient in Padagis's ANDA product, also functions to adjust the osmolality of solutions. Dr. Little accordingly concluded that a person of ordinary skill in the art would consider sodium chloride to perform the same function as mannitol, in the same way, and to achieve the same result. *Id.* at ¶ 499. He further concluded that sodium chloride is insubstantially different from mannitol for purposes of the claimed composition. *Id.* at ¶ 501. Second, Dr. Little explained that mannitol is also a buffering agent, which means that it functions to regulate the pH of the solution. Mannitol performs that function by forming ester bonds with boric acid to create "borate-mannitol complexes." Those complexes bind H+ and OH- ions, thereby resisting changes to pH. Dr. Little stated that other polyols in Padagis's ANDA product, including [redacted] and tartaric acid, also serve as buffering agents by forming borate-polyol complexes in the same way as mannitol does. *Id.* at ¶ 525–533 (incorporating the opinions of Dr. William Jorgensen, another one of Alcon's expert witnesses). For those reasons, Dr. Little concluded that sodium chloride, as well as [redacted], and tartaric acid are equivalent to the claimed "first polyol."

II. LEGAL STANDARD

A district court "shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). A factual dispute is genuine and material if a reasonable factfinder could return a verdict for the nonmoving party. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). For an issue on which the nonmoving party bears the burden of proof at trial, the party seeking summary judgment "bears the initial responsibility of informing the district court of the basis for its motion,

and identifying those portions of 'the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any,' which it believes demonstrate the absence of a genuine issue of material fact." *Celotex Corp. v. Catrett*, 477 U.S. 317, 323 (1986) (quoting Fed. R. Civ. P. 56(c) as of 1986). The burden on the moving party in that situation can be satisfied by "showing," that is, by "pointing out to the district court—that there is an absence of evidence to support the nonmoving party's case." *Id.* at 325. If the moving party carries its burden, the nonmovant must "come forward with specific facts showing that there is a genuine issue for trial." *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 587 (1986) (cleaned up).

The admissibility of expert testimony is governed by the Supreme Court's decision in *Daubert v. Merrill Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), and its progeny. Under *Daubert* and Federal Rule of Evidence 702, the trial court is assigned the task of ensuring that an expert's testimony rests on a reliable foundation and is relevant to the task at hand. *Id.* at 597. In particular, the court must determine whether the reasoning or methodology underlying the expert's testimony is scientifically valid and whether that reasoning or methodology can properly be applied to the facts at issue. *Id.* at 593. The *Daubert* framework applies broadly to "scientific, technical, or other specialized knowledge," and the rules of evidence require the trial judge to determine "whether the testimony has 'a reliable basis in the knowledge and experience of [the relevant] discipline." *Kumho Tire Co. v. Carmichael,* 526 U.S. 137, 149 (1999) (quoting *Daubert*, 509 U.S. at 592).

III. DISCUSSION

Padagis moves for summary judgment of no literal infringement and no infringement under the doctrine of equivalents based on a lack of evidence. Alcon moves to exclude the opinions of

Drs. William Dichtel and Craig Dyar for failure to satisfy Rule 702 and *Daubert*. Padagis's motion is granted in part and denied in part. Alcon's motion is denied.

A. Literal Infringement

Padagis moves for summary judgment of no literal infringement on the ground that Alcon has not pointed to any evidence that Padagis's ANDA product contains mannitol or sorbitol in amounts necessary to infringe the "first polyol" limitation in any of the asserted claims. *See Celotex*, 477 U.S. at 323. The broadest asserted claims require the concentration of the first polyol (mannitol, sorbitol, or a combination of the two) in the claimed composition to be "at least 0.01 w/v % but no greater than 0.5 w/v %." *See* '265 patent at col. 19, ll. 16–20. Claims 1 and 6 through 23 of the '484 patent require the concentration of the first polyol in the composition to be "at least 0.15 w/v % but . . . less than 0.5 w/v %." And claim 3 of the '484 patent requires the concentration of the first polyol in the claimed composition to be "at least 0.25 w/v % but . . . less than about 0.35 w/v %."

With respect to literal infringement, the list of ingredients in Padagis's ANDA product do not include mannitol or sorbitol. However, Padagis's ANDA product is manufactured in the same 300-liter tank as its [redacted], which contains mannitol. For that reason, Padagis acknowledged in an attachment to its ANDA that even though the tank is cleaned between production runs, "[redacted], which could result in some residual mannitol being present in Padagis's ANDA product. *See* Cleaning Process Validation for the 300L Stainless Steel Jacketed Tank, Dkt. No. 185-3, Exh. 3 at 26; *see also* Dkt. No. 204-4, Exh. 4 at 46.

Alcon's expert, Dr. Steven Little, noted that [redacted] of mannitol are used in Padagis's manufacture of [redacted] in the same tank that is used to manufacture Padagis's ANDA product.

Because that amount would constitute [redacted] percent of the contents of the 300-liter tank, and because it would be impossible to remove every trace of mannitol from the tank, no matter how carefully it was cleaned after the tank was used to prepare [redacted], Dr. Little stated that the concentration of mannitol carried over into Padagis's ANDA product would be lower than [redacted] percent but more than 0 percent. Dkt. No. 203 ¶31. Other than setting those outer limits, however, Dr. Little offered no opinion or evidence as to the actual concentration of mannitol in Padagis's ANDA product.

Rather than pointing to evidence that would satisfy its burden to show that Padagis's ANDA product is likely to infringe, Alcon argues that Padagis's ANDA product infringes under 35 U.S.C. § 271(e)(2)(A) because Padagis's ANDA seeks permission to manufacture, use, and sell an infringing product. Alcon's theory is that by acknowledging in its ANDA that there is "[redacted]" from the use of the same tank for both the ANDA product and the [redacted] product, Padagis has in effect sought permission to market a product that will satisfy the "first polyol" limitation of each of the asserted claims and thus will infringe those claims.

Alcon's theory of infringement is predicated mainly on the Federal Circuit's decision in *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271 (Fed. Cir. 2013). In that case, the Federal Circuit reversed a district court's grant of summary judgment of noninfringement where the defendant's ANDA itself provided for an infringing quantity of the contested ingredient. In that case, the defendant argued that even though the ANDA recited quantities of that ingredient that would fall within the scope of the claims, the defendant's internal manufacturing guidelines would yield a product in which the quantity of that ingredient would fall outside the claimed range. *Id.* at 1275.

The claims at issue in *Sunovion* were construed to require less than 0.25 percent of a levorotary enantiomer[3] of the claimed compound; the ANDA called for between 0 and 0.6 percent of the levorotary enantiomer; and the defendant's manufacturing guidelines called for greater than 0.3 percent of that enantiomer. In other words, the ANDA itself covered an infringing range, but the facts showed that the ANDA product would not likely infringe the claims. The Federal Circuit reversed the district court's grant of summary judgment of noninfringement and held that an ANDA that provides for a composition comprising ingredients whose quantities overlap with the ranges claimed in the asserted patents infringes the claims under 35 U.S.C. § 271(e)(2)(A), regardless of what the facts show is likely to occur in practice. *See id.* at 1279 ("What a generic applicant asks for and receives approval to market, if within the scope of a valid claim, is an infringement.").

This case is unlike *Sunovion*, because Padagis's ANDA says nothing about the quantity of mannitol that will be present in its ANDA product, other than to acknowledge that some cross-contamination is possible. Alcon contends that "Padagis's ANDA . . . is seeking approval for a product containing mannitol at the claimed concentrations." Dkt. No. 202 at 11. But the evidence does not support that contention. The documents to which Alcon refers—the cleaning validation report and the sterilization validation report—support an inference that *some* mannitol may be present in Padagis's ANDA product. Those documents, however, say nothing about whether mannitol is present in a concentration between 0.01 w/v percent and 0.5 w/v percent, as is necessary to infringe the claims.

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[3] "Enantiomers" are molecules that are the mirror images of one another, the way one's left hand is the mirror image of one's right hand. One enantiomer of a molecule is called the "dextrorotatory" enantiomer, and the other is called the "levorotatory" enantiomer. Enantiomers often have different properties, so isolation of the desired enantiomer is a common issue in pharmaceutical formulations.

It is not *Sunovion* that governs the analysis in this case, but *Ferring B.V. v. Watson Laboratories, Inc.–Florida* ("*Ferring I*"), 764 F.3d 1382 (Fed. Cir. 2014). In *Ferring I*, as in this case, the ANDA did not expressly address the claim limitations. *See id.* at 1387 (determining that an ANDA specifying the amount of a compound that would dissolve after 60 minutes was "silent" with respect to the claim limitations, which discuss the dissolved dissolution rates at 15, 45, 90, and 120 minutes). The Federal Circuit held that because the ANDA did not definitively establish infringement, the ANDA itself was insufficient to prove infringement without reference to further facts showing that the ANDA product itself would likely satisfy the claim limitations. *Id.* at 1388.

Alcon argues that *Ferring I*, which dealt with a district court's findings of fact and conclusions of law, does not apply to Padagis's motion for summary judgment because there is a material issue of fact regarding whether Padagis's ANDA is silent as to the presence of mannitol. *Ferring I*, however, did not remand for the district court to determine whether the ANDA was silent as to the critical claim limitation. It addressed the ANDA's silence as to the contested limitation and determined, as a matter of law, that the district court erred in finding infringement. Padagis's ANDA says nothing about the concentration of mannitol in the ANDA product. If the dispute over what the ANDA says about the amount of mannitol in Padagis's ANDA product can be called a dispute of fact at all, it is not one on which a reasonable factfinder could find in Alcon's favor. For that reason, I agree with Padagis that *Sunovion* is inapplicable.

Alcon also argues that the Federal Circuit's nonprecedential decision in *Par Pharm., Inc. v. Hospira, Inc.*, 835 F. App'x 578 (Fed. Cir. 2020), supports its argument that by filing its ANDA, Padagis infringed claim 13 of the '265 patent under section 271(e)(2) of the Patent Act. The patent at issue in *Par* claimed a concentration "of about 0.01 to 0.4 mg/mL of a transition metal complexing agent." *Id.* at 582. Citric acid, one of the ingredients listed in the ANDA in *Par*, forms

complexes with transition metals. The citric acid concentration in the ANDA at issue in *Par* was higher than the claimed range; however, both parties' experts treated the amount of transition metal complexing agent as the amount of citric acid necessary to form complexes with all the transition metals in the composition. *See id.* at 586 (explaining that "the amount of transition metal complexing agent is a simple function of the amount of elemental impurities in the form of transition metals in the composition). Thus, the amount of transition metal complexing agent in *Par* depended entirely on the amount of transition metal contaminants available for forming complexes.

Based on batch testing, the district court in *Par* found that there were "clearly metals in Hospira's ANDA product," the concentrations of which were "variable" up to a maximum quantity specified by the ANDA, through the ANDA's express incorporation of the "ICH Q3D limits" for such concentrations. *Par Pharm., Inc. v. Hospira, Inc.*, 420 F. Supp. 3d 256, 278 (D. Del. 2019). At the maximum allowable quantity of transition metals under the ICH Q3D limits, the amount of transition metal complexing agent would infringe the claims. Based on that finding by the district court, the Federal Circuit concluded that Hospira's statement in its ANDA that "its product satisfies the ICH Q3D guidelines" meant that Hospira could "market and sell a product with up to 30 percent of the permitted daily exposure of transition metal impurities,"[4] and thus that the ANDA represented that Hospira's product could contain "sufficient concentrations of elemental impurities such that citric acid would complex with the transition metals in a high enough concentration to

[4] Significantly, Hospira's experts in *Par* admitted that the drug product specification in Hospira's ANDA, which included the statement that the ANDA product "Meets ICH Q3D," constituted a representation as to "what Hospira is asking permission to sell," and that "any batch of [Hospira] ANDA product that meets the ICH Q3D guidelines can be sold." *Par Pharm., Inc. v. Hospira, Inc*., No. 2020-1273 (Fed. Cir.), Joint Appendix 347, 672. Par's expert agreed and testified that under the ANDA Hospira was asserting that it "could sell anything from the range of zero transition metals up to the ICH Q3D guidelines." *Id.* at 426.

satisfy the limitation requiring 'about 0.01 to 0.4 mg/mL of a transitional metal complexing agent." *Par Pharm.*, 835 F. App'x at 586.[5] For that reason, the Federal Circuit held the court's analysis in *Sunovion* to be applicable.

Unlike the ANDA at issue in *Par*, Padagis's ANDA does not specify a permissible amount of mannitol that could be present in its product. Although Dr. Little has stated that the FDA Inactive Ingredients Database permits the presence of up to 4 w/v percent of mannitol, *see* Dkt. No. 203 at ¶ 30, Padagis's ANDA itself does not refer to or incorporate that database, nor does it suggest that the ANDA would authorize it to incorporate mannitol in amounts up to that amount.[6] For that reason, *Par* is inapplicable to this case.[7]

Because this case is one in which it the ANDA does not clearly state whether the ANDA filer intends to manufacture, use, or sell a product falling with the scope of the patentee's claims, "the correct analysis is under *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1570 (Fed.Cir.1997),

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[5] Although the ANDA at issue in *Par* did not expressly state the quantity of transition metal complexing agent that could be present as prescribed by the ANDA, that value could be readily calculated from the quantities of ingredients the ANDA did specify.

[6] Although Dr. Little states that the FDA permits mannitol up to 4 percent, the Inactive Ingredients Database that he refers to lists different "maximum potencies per unit dose" for different types of products. In ophthalmic solutions, those range between 3.3 w/v percent for "suspension/drops" to 5 w/w percent for "gel." *See* U.S. Food and Drug Administration, *Inactive Ingredient Search for Approved Drug Products* (last visited August 29, 2024) https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. It is not clear what standard Dr. Little is referring to when he discusses the 4 percent maximum, as none of the reported maximum tolerances for mannitol are exactly 4 percent.

[7] If the ANDA in this case had referenced the FDA regulations permitting the presence of up to 4 wt/v percent of mannitol, and if Padagis had acknowledged through expert testimony or otherwise that it was claiming the right to under the ANDA to distribute a product containing up to that concentration of mannitol, this case would be more like *Par.* But the ANDA in this case contained no such reference, and Alcon has pointed to no such evidence. The silence of the ANDA in that regard makes this case more like *Ferring*.

not *Sunovion*." *Ferring I*, 764 F.3d at 1387–88. In *Glaxo*, the court held that the ultimate question of infringement under section 271(e)(2)(A) is "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." 110 F.3d at 1569. Where that question is not conclusively answered by the ANDA itself, "the relevant inquiry is whether the patentee has proved by a preponderance of the evidence that the alleged infringer will likely market an infringing product." *Id.* at 1570; *see also Par Pharm., Inc. v. Eagle Pharms., Inc.*, 44 F.4th 1379, 1384 (Fed. Cir. 2022) ("If the ANDA specification does not speak clearly and directly to the question of infringement, courts may look to other relevant evidence, such as data or samples the ANDA filer has submitted to the FDA, to assess whether a proposed product will infringe."); *Ferring B.V. v. Watson Lab'ys, Inc.-Fla.* ("*Ferring II*"), 764 F.3d 1401, 1408 (Fed. Cir. 2014) ("In cases in which the ANDA specification does not resolve the infringement question in the first instance, we have endorsed the district court's reference to relevant evidence, including biobatch data and samples of the proposed generic composition that the ANDA filer had submitted to the FDA."); *Bayer AG v. Elan Pharm. Rsch. Corp.*, 212 F.3d 1241, 1250 (Fed. Cir. 2000) ("[T]he biobatch in *Glaxo* was properly considered because the ANDA specification in that case did not define the compound in a manner that directly addressed the issue of infringement.").

In this case, application of the rule in *Glaxo* requires the court to grant summary judgment of no literal infringement. The short of the matter is that Alcon, which bears the burden of proof on infringement,[8] has not introduced evidence from which a reasonable finder of fact could find

[8] *See Glaxo*, 110 F.3d at 1568 ("[A] patentee seeking relief under § 271(e)(2) must prove by a preponderance of the evidence that what is to be sold will infringe. That burden is not shifted

that the concentration of mannitol introduced into Padagis's ANDA product through cross-contamination is likely to be as much as 0.01 w/v percent of Padagis's composition. Dr. Little's testimony, on which Alcon heavily relies, goes so far as to say that, in theory, the amount of mannitol introduced into Padagis's ANDA product could be as much as nearly all the mannitol that was present in the 300-liter tank when it was used to process [redacted], which would require that nearly all the mannitol in the [redacted] (and none of the other components in that [redacted]) be left in the tank when the tank was cleaned, a wildly unlikely scenario. What Dr. Little did not say was how much mannitol would likely be present after the tank is cleaned in preparation for the manufacture of Padagis's ANDA product. And the absence of any evidence on that issue is fatal to Alcon's literal infringement allegation because, without such evidence, Alcon cannot meet its burden of showing that Padagis's ANDA product is likely to contain enough mannitol to satisfy the "first polyol" limitations in the asserted claims.

Alcon points to three pieces of evidence that purportedly show how an infringing quantity of mannitol may be present in Padagis's ANDA product: a cleaning validation report, Dkt. No. 185-3; a sterilization validation report, Dkt. No. 204-4; and a portion of Dr. Little's report addressing the possibility of cross-contamination. The cleaning validation report implies that Padagis tests for the possibility of cross-contamination of active ingredients but does not test for cross-contamination of excipients such as mannitol. The sterilization validation report expressly identifies mannitol as one of the excipients introduced into the shared tank during the manufacture of the [redacted]. *See* Dkt. No. 204-4 at PADBRI0000226. And Dr. Little's declaration and expert

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under § 271(e)(2)."). *See also Under Sea Indus., Inc. v. Dacor Corp.*, 833 F.2d 1551, 1557 (Fed. Cir. 1987) ("The burden always is on the patentee to show infringement."); *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008) ("Neither [the] burden to prove infringement nor [the] burden to prove invalidity . . . ever shifts to the other party.").

report, *see generally* Dkt. No. 203; Dkt. No. 185-2, Ex. 2 at ¶ 91, state that it is impossible to remove 100 percent of any compound through cleaning, so some indeterminate amount of mannitol will necessarily remain in the shared tank and thus be present in Padagis's ANDA product. *See* Dkt. No. 185-2, Ex. 2 at ¶¶ 86–105.

Dr. Little's expert report goes into substantial detail about how *some* mannitol is likely to be found in Padagis's ANDA product. That discussion, however, does not speak to the likely quantity of mannitol in Padagis's ANDA product—only its existence. The report omits any discussion of the quantity of such mannitol, perhaps because Dr. Little's opinion was presented in the context of claim 1 of the '256 patent, which is no longer asserted and does not include a lower limit on the claimed range of mannitol. In his discussion of infringement of the currently asserted claims, however, Dr. Little merely incorporated his earlier non-quantitative analysis. *See id.* at ¶ 187 ('256 patent, claim 13), ¶ 300 ('484 patent, claim 1), ¶ 376 ('484 patent, claim 15), ¶ 441 ('484 patent, claim 22). Alcon has not identified any portion of Dr. Little's report in which he stated the opinion that Padagis's ANDA product will contain at least 0.01 w/v percent mannitol, the lowest claimed quantity.

In summary, Alcon has not met its burden of directing the court to evidence from which a reasonable factfinder could return a verdict of literal infringement in Alcon's favor. *See Anderson*, 477 U.S. at 248. For that reason, summary judgment of no literal infringement is granted as to all asserted claims.

B. Doctrine of Equivalents

Alcon argues that even if the court were to grant summary judgment of no literal infringement, there is a factual dispute regarding infringement under the doctrine of equivalents. Dr. Little's expert report states that sodium chloride and various polyols found in Padagis's ANDA

product are equivalent to mannitol because they perform the same function as mannitol in the same way and achieve the same result. *See generally Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950).

As an initial matter, the parties disagree about what the limitation at issue is for purposes of the doctrine of equivalents analysis. Alcon argues that the limitation at issue is simply the identity of the ingredient, whereas Padagis argues that the concentration of the first polyol is also important. The core issue here is whether the purportedly equivalent ingredient performs the same function as mannitol or sorbitol in the composition and achieves the same result. *See Graver Tank*, 339 U.S. at 608; *see also Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 40 (1997) (explaining that the core question is "whether a substitute element matches the function, way, and result of the claimed element, or whether the substitute element plays a role substantially different from the claimed element"). The main function of mannitol and sorbitol, according to the patents, is to "enhance anti-microbial activity in the presence of a preservative." *See* '484 patent at col. 2, ll. 53–56. The extent to which mannitol or sorbitol forms those complexes is determined by their concentrations. While the purported equivalent need not necessarily be present in the claimed concentrations of mannitol or sorbitol, it must achieve the same result as the claimed concentrations of those ingredients. Thus, the concentration of a proposed equivalent is an important factor in the analysis, but the concentration of an equivalent need not necessarily fall within the claimed range for mannitol or sorbitol.

Only one of Alcon's doctrine of equivalents theories contains a triable issue of fact. As explained in more detail below, Dr. Little's testimony fails to show that sodium chloride performs two key functions of mannitol in the claimed formulation—increasing antimicrobial activity and buffering capacity. And [redacted] are present only as

impurities. Because Alcon has pointed to no evidence regarding their concentrations in the ANDA product, there is no basis for finding that any of those three compounds are equivalent to the amount of mannitol required by the claims. However, I conclude that Dr. Little has presented a colorable contention that tartaric acid could be considered equivalent to mannitol in the claimed compositions. Thus, summary judgment of no infringement under the doctrine of equivalents will be denied with respect to the asserted equivalence of tartaric acid to the claimed first polyol.

1. Equivalence of Sodium Chloride

Alcon's first doctrine of equivalents position is that sodium chloride performs the same function as mannitol in Padagis's ANDA product. According to Alcon, mannitol's function is as a tonicity agent, meaning that its role is to adjust the osmolality of the solution. Sodium chloride is a standard tonicity agent, and therefore is equivalent to mannitol with respect to that function. Alcon's argument is unpersuasive, however, because no reasonable factfinder could conclude that mannitol's main function is as a tonicity agent. As explained in the patents, mannitol's main function is "to enhance anti-microbial activity in the presence of a preservative" by forming complexes with borate that have antimicrobial properties. *See* '484 patent at col 2, ll. 53–56. Additionally, mannitol increases the buffering capacity of the solution. Alcon makes no attempt to explain how sodium chloride increases anti-microbial activity and increases buffering by forming complexes with borate. For that reason, no reasonable factfinder could conclude that sodium chloride is equivalent to mannitol in the claimed compositions.

Alcon's core argument in its brief is that summary judgment should not be granted, because there is a material dispute of fact regarding the function performed by mannitol. Alcon concedes that the patent indicates that the first polyol can enhance antimicrobial activity and increase buffering. *See* Dkt. No. 202 at 25 (citing '265 patent at col 2, ll. 53–54; *id.* at col 4, ll. 59–62).

Alcon argues, however, that Padagis's own representations to the FDA show that mannitol is a tonicity agent. Dkt. No. 204-5, Ex. 5 at PADBRI0001204 (stating that the ANDA product "excludes mannitol (a tonicity agent)."").

Alcon's extrinsic evidence is somewhat probative of the role mannitol performs in the claimed composition. *See Intendis GMBH v. Glenmark Pharms. Inc.*, USA, 822 F.3d 1355, 1361–62 (Fed. Cir. 2016) (affirming the district court's use of statements made by an ANDA applicant to the FDA to determine the function of a claim element, where the patent itself did not state the element's function). But extrinsic evidence cannot supersede the clear statement in the patents themselves that mannitol's function is to form complexes with borate that have desirable antimicrobial and buffering properties. *See Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 141 F.3d 1084, 1090–91 (Fed. Cir. 1998) (vacating a preliminary injunction where the district court's findings concerning the functions performed by a claim limitation, for purposes of the doctrine of equivalents, were contrary to the functions described in the specification). The formation of borate-polyol complexes is central to the present invention. That much is clear from the patents' titles alone: "Aqueous Pharmaceutical Compositions Containing Borate-Polyol Complexes." The intrinsic record is clear that substituting table salt for the first polyol, one of the two titular claim elements, does not yield an equivalent formulation.

Because the patent clearly states that mannitol increases antimicrobial activity and increases buffering by forming complexes with borate, no reasonable juror could conclude that sodium chloride is equivalent to mannitol purely based on their shared function as a tonicity agent. Because there is no material dispute of fact on this issue, *see Anderson*, 477 U.S. at 248, Padagis is entitled to summary judgment with respect to Alcon's theory of equivalents based on sodium chloride.

2. Equivalence of [redacted], and Tartaric Acid

Alcon's alternative doctrine of equivalents position is that a combination of [redacted] and tartaric acid perform the same function as mannitol and sorbitol in the claimed compositions. None of those compounds are listed in the ANDA; however, Dr. Little explained in his expert report that [redacted] are likely present as impurities in the [redacted] that Padagis uses in manufacturing the ANDA product. Tartaric acid and its conjugate base, tartrate, are both present through the introduction of brimonidine tartrate, one of the two active pharmaceutical ingredients in Padagis's ANDA product. All four of those compounds are polyols that increase the buffering capacity and antimicrobial activity of the composition by forming complexes with borate. *See* Dkt. No. 185-2 at ¶¶ 522–545. At a minimum, there is a genuine dispute of fact regarding whether a combination of [redacted], and tartaric acid are equivalent to the claimed first polyol.

Because [redacted] may be present only as impurities, however, the possibility of their inclusion is insufficient to establish infringement for the same reason that mannitol contamination cannot establish literal infringement. Alcon has not quantified the extent to which those impurities will likely be present in Padagis's product, and it cannot establish that some unknown concentrations of [redacted] achieve the same result as the claimed quantities of mannitol or sorbitol. Simply noting the maximum tolerance for impurities set by Padagis's [redacted] supplier does not suffice to prove the concentrations of those compounds that are likely to be present in Padagis's ANDA product.

The more challenging aspect of Alcon's position relates to tartaric acid. Tartrate, the conjugate base of tartaric acid, is added to Padagis's ANDA product as part of an active pharmaceutical ingredient, brimonidine tartrate. At the pH of Padagis's ANDA product, most of the tartrate added will be in its tartaric acid form. Dr. Little stated that in his opinion both tartrate and tartaric acid are equivalent to the first polyol of the claims. *See* Dkt. No. 185-2 at ¶ 505, n.6 (explaining that tartaric acid and tartrate are interchangeable for purposes of his analysis).

Unlike mannitol, [redacted], the amount of tartrate in Padagis's ANDA product is quantifiable. Brimonidine tartrate is listed in the ANDA as accounting for 0.2 w/v percent of the total formulation. Of that amount, 33.6 percent, or 0.067 w/v percent of the overall ANDA product, is tartrate or tartaric acid.[9] Some of the asserted claims call for 0.01 to 0.5 w/v percent of a first polyol, *see, e.g.,* '256 patent at col. 19, ll. 16–36; and others call for 0.15 to 0.5 w/v percent of that polyol, *see, e.g.,*'484 patent at col. 17, ll. 6–7; *id.* at col. 17, ll. 59–60; *id.* at col. 18, ll. 35–36.

The challenge regarding Alcon's argument is that Alcon has not demonstrated how it will prove that 0.067 w/v percent of tartrate is equivalent to 0.01 to 0.5 w/v percent mannitol. Although Dr. Little stated in his report that tartaric acid forms complexes with borate that have antimicrobial and buffering properties, he did not express an opinion as to whether the results achieved by the tartaric acid in Padagis's ANDA product are equivalent to the results achieved by the claimed mannitol concentrations. *See, e.g.*, Dkt. No. 185-2 at ¶ 543 (addressing the result of the first polyol

[9] The amount of tartrate in Padagis's ANDA product can be easily calculated. Brimonidine has a molecular weight of 292.14 g/mol. Tartrate has a molecular weight of 148.07 g/mol. There is a 1 to 1 ratio between brimonidine and tartrate in brimonidine tartrate. Tartrate therefore accounts for 148.07/(148.07+292.14) = 33.6 percent of the brimonidine tartrate by mass, which is 0.067 w/v percent of the overall ANDA product.

limitation qualitatively as "enhancing antimicrobial activity," but not quantifying the degree of enhancement); *id* at ¶ 536 (same with respect to buffering capacity). A trivial increase to antimicrobial activity and buffering capacity would not be equivalent to the results achieved by the claimed concentrations of mannitol.

Although Alcon has not identified any portion of an expert report that directly addresses whether tartaric acid achieves a result quantitatively equivalent to the results of the claimed concentration of mannitol, a reasonable factfinder may still be able to find in Alcon's favor. In his report, Dr. Little directly stated that tartaric acid performs the same function, in the same way, as mannitol. *See* Dkt. No. 185-2 at ¶¶ 522–545. That opinion, combined with the fact that the concentration of tartaric acid in the ANDA falls within the claimed concentrations of mannitol, makes it plausible that 0.067 w/v percent concentration of tartrate achieves the same result as the claimed concentration of mannitol in the formulation.

Padagis next argues that summary judgment should be granted on the doctrine of equivalents issue because Alcon dedicated the subject of Padagis's ANDA product to the public by disclosing Composition S in the patents. *See generally Johnson & Johnston Assocs. Inc. v. R.E. Serv. Co.*, 285 F.3d 1046, 1055 (Fed. Cir. 2002) (en banc) (ruling that a steel sheet could not be equivalent to an aluminum sheet, where the patent's specification disclosed sheets made of both materials, but the claim limitation referred only to aluminum sheets).

Johnson does not govern this case, because Composition S does not include tartaric acid. Padagis argues that Composition S is designed to be used in conjunction with an active pharmaceutical ingredient, and that brimonidine tartrate is listed in the patents as one of the "examples of therapeutic agents that may be contained in the ophthalmic compositions" of the invention. I agree with Padagis that Composition S is intended to be used in combination with an

active ingredient. But I disagree that the disclosure-dedication rule necessarily bars recapture of Composition S plus an active ingredient. Whether that is true depends on subsidiary facts, which neither party has developed.

Although "[t]he application of the disclosure-dedication doctrine is a question of law," *Eagle Pharms. Inc. v. Slayback Pharma LLC*, 958 F.3d 1171, 1177 (Fed. Cir. 2020), the application of the doctrine in particular cases, like other questions of law, may depend on subsidiary factual findings. *See, e.g.*, *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1326 (Fed. Cir. 2016) (obviousness); *In re Morsa*, 713 F.3d 104, 109 (Fed. Cir. 2013 (enablement); *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009) (whether a printed publication is prior art). The standard for determining whether a disclosure in the patent is dedicated to the public hinges on what a person of ordinary skill in the art would understand. *See PSC Computer Prods., Inc. v. Foxconn Int'l, Inc.*, 355 F.3d 1353, 1360 (Fed. Cir. 2004). "[I]f one of ordinary skill in the art could understand the unclaimed disclosed teaching upon reading the written description, the alternative matter disclosed has been dedicated to the public. *Id.*; *Toro Co. v. White Consol. Indus., Inc.*, 383 F.3d 1326, 1334 (Fed. Cir. 2004). Neither party's brief addresses what a person of ordinary skill in the art would understand. In some cases, the patents themselves may be sufficiently clear to decide the issue. *See, e.g., Eagle Pharms.*, 958 F.3d at 1178. Here, however, it is not readily apparent what a person of ordinary skill in the art would understand the patents to disclose with respect to suitable active ingredients to be used with Composition S. For that reason, summary judgment on this issue is inappropriate.

Padagis also argues that prosecution history estoppel bars the recapture of tartrate as an equivalent to mannitol, at least with respect to the claims of the '484 patent. Prosecution history estoppel presumptively applies where a patent applicant narrows its claims through amendment

during prosecution. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 740 (2002). Subject to exceptions, such narrowing of claim scope results in "disclaimer of the territory between the original claim and the amended claim," which prevents recapture of the disclaimed claim scope through the doctrine of equivalents. *Id.* During the prosecution of the '484 patent, the applicant sought claims to mannitol or sorbitol without any concentration limitation. *See* Dkt. No. 185-12, Ex. 12 at ALCON_SIMBRINZA_00001046. After the initial claims were rejected, the applicant amended the claims to require between 0.15 and 0.5 w/v percent mannitol or sorbitol and explained that "high concentrations of a strong buffer such as borate with mannitol and/or sorbitol can inhibit the ability of the eye to return to physiologic pH," so lower concentrations are desirable. *Id.* at ALCON_SIMBRINZA_00001131.

Although the'484 patent was narrowed by amendment, the "territory between the original claim and the amended claim," *Festo*, 535 U.S. at 740, does not include a composition containing tartaric acid instead of mannitol. Such a composition is outside both the original and amended claims, so it cannot be said to have been surrendered during prosecution. For that reason, prosecution history estoppel does not bar Alcon's doctrine of equivalents theory regarding tartaric acid. In summary, a material dispute of fact exists with respect to the equivalence between tartaric acid and mannitol, so summary judgment is denied on that issue.

C. Exclusion of Expert Testimony

Alcon requests that the court exclude various opinions of Padagis's expert witnesses, Drs. Dichtel and Dyar. Alcon contends that because both experts lack a background in microbiology, they are unqualified to offer opinions regarding the antimicrobial activity and preservative efficacy of the pharmaceutical compositions at issue in this case. Specifically, Alcon seeks the exclusion of paragraphs 74–85 of Dr. Dichtel's opening report, Dkt. No. 187-2; paragraphs 3–5 of Dr.

Dichtel's supplemental report, Dkt. No. 187-4; paragraphs 234, 261, 284, and 305 of Dr. Dyar's rebuttal report, Dkt. No. 187-9; and paragraphs 11 and 23 of Dr. Dyar's supplemental report, Dkt. No. 187-8. I find that Drs. Dichtel and Dyar are reasonably qualified to offer opinions on the antimicrobial effects of the compositions at issue, so Alcon's motion will be DENIED.

The Federal Rules of Evidence allow a witness "qualified as an expert by knowledge, skill, experience, training, or education" to testify to "assist the trier of fact to understand the evidence or to determine a fact in issue." Fed. R. Evid 702; *see generally Daubert*, 509 U.S. at 579. The Third Circuit interprets the qualification requirement "liberally" and has held that "a broad range of knowledge, skills, and training qualify an expert as such." *Calhoun v. Yamaha Motor Corp., U.S.A.*, 350 F.3d 316, 321 (3d Cir. 2003); *see also Sonos, Inc. v. D & M Holdings Inc.*, 297 F. Supp. 3d 501, 508 (D. Del. 2017).

Even if Alcon is correct that an expert with experience in microbiology would be more qualified to testify regarding the antimicrobial properties of the compositions, that is not a reason to exclude the opinions of Drs. Dichtel and Dyar. "[W]itnesses may be competent to testify as experts even though they may not, in the court's eyes, be the 'best' qualified. Who is 'best' qualified is a matter of weight upon which reasonable [factfinders] may disagree." *Holbrook v. Lykes Bros. S.S. Co.*, 80 F.3d 777, 782 (3d Cir. 1996). "[I]nsistence on a certain kind of degree or background is inconsistent with [the Third Circuit's] jurisprudence." *In re Paoli R.R. Yard PCB Litig.*, 916 F.2d 829, 855 (3d Cir. 1990) (reversing the exclusion of three experts' opinions, none of whom had "the degree or training which the district court apparently thought would be most appropriate"). Generally speaking, "arguments about an expert's qualifications relate more to the weight to be given the expert's testimony than to its admissibility." *Holbrook*, 80 F.3d at 782.

The Third Circuit's instruction that challenges to expert qualifications relate more to weight than admissibility is particularly powerful in the context of a bench trial. "[C]ourts in this circuit and others have acknowledged that the gatekeeping obligation provided for in *Daubert* is less pressing in the context of a bench trial." *LG Display Co. v. AU Optronics Corp.*, 265 F.R.D. 189, 195 (D. Del. 2010) (citing *United States v. Brown*, 415 F.3d 1257, 1268 (11th Cir. 2005); *Deal v. Hamilton County Bd. of Educ.*, 392 F.3d 840, 852 (6th Cir. 2004); *Gibbs v. Gibbs*, 210 F.3d 491, 500 (5th Cir. 2000); *Gannon v. United States*, 571 F. Supp. 2d 615, 616 (E. D. Pa. 2007)). Courts in a bench trial may judge the reliability of expert testimony "on a full record made at trial." *Sanofi-Aventis U.S. LLC v. Merck Sharp & Dohme Corp.*, No. CV 16-812-RGA, 2018 WL 2422003, at *2 (D. Del. May 29, 2018) ("While I acknowledge the 'gate-keeper' function of a federal trial judge, it is not so important that it be done pretrial when the trial is a bench trial.").

Dr. Dichtel is a chemistry professor at Northwestern University with expertise in boron chemistry. *See* Dkt. No. 200-1, Ex. 4 at ¶¶ 7-16. Dr. Dyar is an expert in drug formulation with a degree in pharmaceutical science. *Id.* Ex. 6 at ¶ 8. Both experts have "knowledge, skill, experience, training, or education" relevant to the question of whether specific boron-polyol complexes will have antimicrobial properties. Their testimony on that subject is therefore admissible.

The more difficult issue is whether Dr. Dichtel can also testify about the biological pathways by which borate-polyol complexes inhibit microbial growth. In paragraphs 81–83 of his report, Dkt. No. 187-2, Dr. Dichtel challenges Alcon's microbiology expert's opinions regarding various "transport mechanisms" in microbial cells relevant to the uptake of borate-polyol complexes. Although a microbiologist may be better qualified to testify about the biological pathways by which those complexes inhibit microbial growth, I find that Dr. Dichtel's professional

experience enables him to offer an opinion on the subject that will help the court decide the relevant factual issues. For that reason, and considering the liberal standard for expert qualifications applied by the Third Circuit, I find Dr. Dichtel sufficiently qualified to testify on that subject.

Because I find that the challenged opinions are sufficiently useful to justify admission under Rule 702 and *Daubert*, Alcon's motion to exclude those opinions is denied.

IV. CONCLUSION

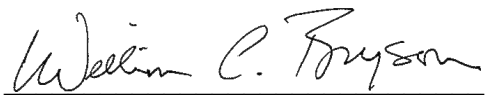
Padagis's motion for summary judgment is GRANTED IN PART. Summary judgment of no literal infringement is granted. Summary judgment of no infringement under the doctrine of equivalents is granted with respect to Alcon's theories that sodium chloride, [redacted] are equivalent to mannitol. Summary judgment is denied with respect to Alcon's theory that tartaric acid is equivalent to mannitol. Alcon's motion to exclude various opinions of Padagis's experts is DENIED.

In light of the significant simplification of the case as a result of this order, the length of the trial will be reduced from five days to four and the parties' time for their trial presentations will be reduced from 16 hours per side to 12 hours per side.

Although it is not apparent that anything in this order reveals confidential information, this order has been filed under seal because the parties' briefs and exhibits pertaining to the present motions were filed under seal. Within three business days of the issuance of this order, the parties are directed to advise the court by letter whether they wish any portions of the order to remain under seal. Any request that portions of the order should remain under seal must be supported by a particularized showing of need to limit public access to those portions of the order.

IT IS SO ORDERED.

SIGNED this 29th day of August, 2024.



WILLIAM C. BRYSON
UNITED STATES CIRCUIT JUDGE