IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALCON INC., ALCON VISION, LLC, and ALCON LABORATORIES, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 22-1422-WCB
PADAGIS ISRAEL PHARMACEUTICALS LTD., PADAGIS US LLC, and PADAGIS LLC,	)	**FILED UNDER SEAL**
Defendants.	)	

FINDINGS OF FACT AND CONCLUSIONS OF LAW

This is a Hatch-Waxman Act case. Plaintiffs Alcon Inc., Alcon Vision, LLC, and Alcon Laboratories, Inc., (collectively, "Alcon") have sued defendants Padagis Israel Pharmaceuticals Ltd., Padagis US LLC, and Padagis LLC (collectively, "Padagis") for patent infringement under 35 U.S.C. § 271(e)(2). Padagis argues that it does not infringe the asserted claims and that the asserted claims are invalid for obviousness under 35 U.S.C. § 103 and for failure to satisfy the written description requirement of 35 U.S.C. § 112(a).

I. Procedural Background

A. The Hatch-Waxman Act

The Hatch-Waxman Act is the name commonly used to refer to the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. §§ 355, 360(cc) and 35 U.S.C. §§ 156, 271, 282), as amended by the Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066. The Hatch-Waxman Act was designed to strike a balance between two competing policy interests: (1) to

induce pioneering research and development of new drugs; and (2) to enable competitors to bring low-cost generic versions of those drugs to market rapidly if those drugs are not entitled to patent protection. *See Andrx Pharms., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1371 (Fed. Cir. 2002). To promote those objectives, the Hatch-Waxman Act provides for a prompt determination of whether drugs made and sold by brand-name pharmaceutical companies are protected by valid patents. If the patents are held to be infringed and not invalid, the covered drugs cannot be made and sold by generic manufacturers until the patents expire. If the patents are held to be invalid or not infringed, the Act provides a mechanism for prompt approval of the generic versions of the drugs by the U.S. Food and Drug Administration ("FDA"), which regulates the sale of pharmaceutical drugs in this country.

To obtain the necessary FDA approval to market a new drug, a pharmaceutical company must file a New Drug Application ("NDA"). That application is designed to show the FDA, through rigorous testing procedures, that the drug is safe and effective for its proposed uses. After considering the application, and often after extended negotiations with the pharmaceutical company, the FDA may grant the application and authorize the company to market the drug for particular indications. The company is restricted to marketing the drug for those indications, as dictated by FDA regulations that govern both labeling and advertising for all prescription drugs. *See* 21 C.F.R. §§ 201.1–201.327 (labeling); *id.* § 202.1 (advertising).

To speed up the approval process for generic drugs, the Hatch-Waxman Act provides that a generic drug manufacturer may submit an Abbreviated New Drug Application ("ANDA") for approval by the FDA. If the generic company intends to market a drug that is bio-equivalent to the first pharmaceutical company's approved drug, the ANDA may rely on the safety and efficacy studies previously submitted as part of the first company's NDA.

Under the Hatch-Waxman Act, NDA holders are required to notify the FDA of all patents that "claim [] the drug for which the [NDA] applicant submitted the application . . . and with respect to which a claim of patent infringement could reasonably be asserted." 21 U.S.C. § 355(b)(1), (c)(2). The FDA lists such patents in a publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations," which is commonly referred to as the "Orange Book." *See Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1318 (Fed. Cir. 2012); *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1045 (Fed. Cir. 2010).

The Hatch-Waxman Act creates what is referred to as an "artificial" type of infringement that allows for the adjudication of the parties' rights regarding patents that would be infringed if the ANDA were issued and the generic product made, used, or sold in this country. *See Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); *Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1351 (Fed. Cir. 2004). In particular, 35 U.S.C. § 271(e)(2)(A) provides that it shall be an act of patent infringement to submit an ANDA "for a drug claimed in a patent or the use of which is claimed in a patent" if the purpose of the submission of the ANDA is to obtain approval to engage in the commercial manufacture, use, or sale of the drug claimed in the patent, or the use of which is claimed in the patent, before the patent's expiration.

B. The Proceedings in This Case

Alcon obtained FDA approval for an ophthalmic product containing a preservative composition, which Alcon now markets under the brand name Simbrinza®. Simbrinza® is indicated for the treatment of elevated intraocular pressure, a condition associated with glaucoma, a disease that can lead to loss of sight.

Padagis subsequently submitted an ANDA to the FDA seeking approval to market a generic equivalent of Simbrinza®. On October 27, 2022, Alcon filed this action, alleging that

Padagis had infringed claims from U.S. Patent No. 9,044,484 ("the '484 patent") and U.S. Patent No. 9,421,265 ("the '265 patent") under 35 U.S.C. § 271(e)(2)(A) by the act of filing an ANDA for its generic product. Following supplemental claim construction in May 2024, Dkt. No. 152, the parties stipulated to noninfringement of claims 1–12 of the '265 patent. Dkt. No. 182. Prior to trial, Padagis moved for summary judgment of non-infringement of the asserted claims of the '484 patent, and I granted that motion. Dkt. No. 225. Padagis subsequently withdrew its invalidity counterclaims as to the '484 patent, with Alcon's agreement that it could re-raise those counterclaims if the noninfringement rulings on Alcon's corresponding claims were reversed, vacated, amended, or otherwise altered on appeal. Dkt. No. 240. Padagis also moved for summary judgment of non-infringement of the remaining claims of the '265 patent. I granted that motion in part, finding there was no literal infringement of those claims, but I denied the motion with respect to Alcon's theory of infringement under the doctrine of equivalents. Dkt. No. 225. Therefore, with respect to infringement and invalidity, the parties addressed at trial only the issues of infringement under the doctrine of equivalents and the validity of the remaining claims of the '265 patent. The '265 patent is listed in the Orange Book in connection with Alcon's product Simbrinza®.

At issue at trial were claims 13–19 of the '265 patent. They recite:

> 13. 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.

14. A composition as in claim 13 wherein the resistance provided by the composition to normalization of tear pH after instillation in the eye is less than 15 µl of 1 M NaOH/mL of composition.

15. A composition as in claim 13 wherein the viscosity of the suspension is greater than 20 cps but less than 500 cps with the viscosity of the suspension being measured at a high shear rate of 120 sec-1 at room temperature.

16. A composition as in claim 15 wherein the suspension is redispersed with no more than 15 seconds of vigorous shaking.

17. A composition as in claim 13 wherein the composition is free of any quinolone anti-infective or anti-biotic therapeutic agent.

18. A composition as in claim 13 wherein the composition is configured for administration to the eye of the [sic] mammal repeatedly for an extend [sic] period of time of [sic] and is administered at least once a week and wherein the eye of the mammal has been diagnosed with an eye disorder that is suitably treated with chronic administration of the therapeutic agent.

19. A composition as in claim 18 wherein the eye disorder is elevated intraocular pressure.

'265 patent at 19:16–20:14.

The parties stipulated that for purposes of infringement of claims 13–19 the only limitation in dispute was "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%." Dkt. No. 265. They also agreed that for the purposes of proving obviousness, independent proof would need to be provided to demonstrate the obviousness of

claims 14 and 15, but that the obviousness of claims 16–19 would rise or fall with the obviousness of claim 13. *Id.*

II. The Background of the Invention

Many ophthalmic drug products are applied directly to a patient's eye or are applied to devices that will come into contact with the eye, such as contact lenses. These drug products must be sterile. Although such a composition can be manufactured under sterile conditions, the sterility of the product may be compromised once the product's packaging is opened. This compromised sterility risks contamination and potential injury to the patient's eye.

The risk of contamination is heightened in multi-dose products that are used multiple times by the patient. One method of preventing contamination is to include a chemical agent in the composition that inhibits the proliferation of microbes. Such agents are known as anti-microbial preservatives. The problem with such preservatives is that ophthalmological compositions may directly or indirectly contact the patient's cornea, which is particularly sensitive to chemical agents. Therefore, the industry preference is to use preservatives that are relatively non-toxic to the cornea and to administer them at low concentrations. But that approach comes with its own challenges, as low concentrations of preservatives may be insufficient to achieve the desired anti-microbial effect. Accordingly, it can be difficult to identify an optimal concentration that balances anti-microbial efficacy against the potential toxic effects of the preservative.

One commonly used preservative is benzalkonium chloride (commonly referred to as "BAC" or "BAK"). Although BAC is less toxic at lower concentrations, it can lose its anti-microbial efficacy at those lower concentrations. Researchers at Alcon sought to address that problem by developing a preservative system that would enhance the anti-microbial effects of

BAC so that BAC could be used in ophthalmic compositions at less toxic concentrations while still providing sufficient anti-microbial efficacy.

The named inventor on the '265 patent is Dr. Bhagwati Kabra. While employed by Alcon, Dr. Kabra sought to develop ophthalmic compositions using brinzolamide and brimonidine. Brinzolamide and brimonidine are both active ingredients that can be effective in treating intraocular pressure and glaucoma. Dr. Kabra was responsible for developing the preservative system for the formulation. He explained that glaucoma products typically use BAC as the preservative agent, but that by 2004 ophthalmologists were expressing a desire for glaucoma products with preservative agents other than BAC, as it was known that prolonged use of BAC could be harmful to the eye. Tr. 20:15–21:8.

At around that time, Dr. Kabra was also experimenting with the formulation of another Alcon product known as Travatan Z®. Tr. 21:16–22:1. Specifically, he was asked to develop an alternative preservative system so that BAC could be removed from Travatan Z®, and he was able to do so. Tr. 22:20–24. However, while the reformulated product passed the United States standard for anti-microbial efficacy, it did not pass either of the two European standards. Tr. 23:9–17. The United States standard is found in the United States Pharmacopeia and the European standards are found in the Pharmacopoeia Europaea. The European standards are known as Pharmacopoeia Europaea A and Pharmacopoeia Europaea B.

In an effort to develop a product that would pass the Pharmacopoeia Europaea standards, Dr. Kabra began experimenting with introducing small amounts of BAC into his formulation. Tr. 31:14–20. He initially added BAC at a concentration of 0.004%, but he found that the product still did not pass the Pharmacopoeia Europaea standards. Tr. 33:9–22, 36:1–4. Dr. Kabra then began removing other ingredients from the formulation so that he could focus on optimizing preservative

effectiveness. Tr. 36:7–16. Pertinently, he removed zinc chloride from the formulation so that BAC was the only preservative that remained. Tr. 36:7–16. He did not expect that formulation to pass the Pharmacopoeia Europaea standards because BAC was traditionally used at a concentration of 0.01% and in that formulation he was using a concentration of only 0.002%. Tr. 37:3–38:6. But he thought the results might help him design better experiments moving forward. Tr. 36:21–37:2. To his surprise, one of the formulations he tried with a low concentration of BAC passed the United States standard and both Pharmacopoeia Europaea standards. That formulation contained BAC at a concentration of 0.002% and also contained boric acid, sorbitol, and propylene glycol as ingredients.[1] Tr. 39:6–40:3.

Between 2005 and 2006, Dr. Kabra incorporated those findings into his development work with an eyedrop designed to treat allergy symptoms. In that work, he tested a formulation that had a low concentration of BAC, boric acid, and two polyols (sorbitol and propylene glycol) against a formulation that had a low concentration of BAC, boric acid, and only one polyol (sorbitol). He ran that test to determine whether it would be possible to remove one polyol, thereby reducing the number of excipients needed. Tr. 40:20–42:4. He found that the formulation with two polyols continued to pass the standards, but that the formulation with only one polyol did not. Tr. 42:9–18.

In 2008 and 2009, Dr. Kabra began experimenting with using various concentrations of BAC in ophthalmic suspensions containing the active ingredient roscovitine. Tr. 51:2–11. During his testimony, Dr. Kabra explained that in solutions, the active ingredient particles dissolve in the formulation, whereas in suspensions the active ingredient particles do not dissolve, but are suspended in the formulation until they gradually settle at the bottom of the container holding the

[1] I understand Dr. Kabra to be attributing the success he had with that formulation to the removal of zinc chloride. *See* Tr. 52:22–53:8.

suspension. Tr. 51:16–52:2. To combat that settling effect, he testified, formulators typically add a suspending agent, which keeps the particles dispersed throughout the composition. Tr. 52:3–10. Dr. Kabra noted that a suspending agent could cause problems by interacting with the preservative agent. He explained that the suspending agent is a polymer chain containing multiple negative charges, while the preservative has one or more positive charges; as a result, the two can interact, making the preservative less effective. Tr. 52:10–53:8. Based on that interaction, Dr. Kabra expected to have difficulty getting the roscovitine suspension to pass the preservative effectiveness tests. Nevertheless, he began testing formulations containing low BAC concentrations together with two polyols, and he found that those formulations passed all three necessary standards. Tr. 56:21–57:10.

Those results informed Dr. Kabra's work with the composition containing brinzolamide and brimonidine that had begun in 2004. Specifically, Dr. Kabra tested a formulation containing brinzolamide and brimonidine together with a low concentration of BAC, boric acid, and two polyols. Tr. 65:21–66:1. He testified that he was excited to find that the formulation with the low concentration of BAC passed the United States standard and both Pharmacopoeia Europaea standards. Tr. 67:11–20. Eventually, Alcon decided to seek FDA approval for a brimonidine tartrate/brinzolamide suspension containing a 0.003 w/v % concentration of BAC, a 0.3 w/v % concentration of boric acid, a 0.4 w/v % concentration of carbomer 974P (a carboxyvinyl polymer that serves as a suspending agent), and two polyols (a 0.3 w/v % concentration of mannitol and a 0.75 w/v % concentration of propylene glycol). DTX 1169. That formulation is currently marketed as Simbrinza®. Based on the work leading to the development of Simbrinza®, Alcon also sought to patent a more general composition containing two polyols, borate, BAC, and a therapeutic agent. The '265 patent issued as a result.

In addition to the other components, the claims of the '265 patent all require a first polyol, which can be mannitol, sorbitol, or a combination of both, in a concentration of between 0.01 w/v % and 0.5 w/v %. The patent defines a polyol as a molecule that has at least two hydroxyl groups (also commonly referred to as -OH groups) on two adjacent carbon atoms that are not in trans configuration relative to each other. '265 patent at 4:7–10. The specification explains that the purpose of the first polyol is (1) to increase the buffering capacity of the compositions and (2) to enhance the anti-microbial activity in the presence of a preservative. '265 patent at 4:59–62, 7:19–23.

Mannitol and sorbitol are closely related molecules. They have the same chemical formula, $C_6H_{14}O_6$, the same atomic weight, and very similar structures. Structurally, they differ only with respect to the orientation of the -OH group on the second carbon atom.

In this proceeding, the parties have treated mannitol as the representative first polyol molecule, *see, e.g.*, Tr. 427:6–11, and Alcon's post-trial briefing addresses mannitol and sorbitol collectively. Accordingly, for purposes of both the infringement and the invalidity analysis, I will address the molecules collectively and for simplicity will refer to the first polyol as "mannitol" rather than "mannitol, sorbitol, or a combination thereof."

III. Persons of Ordinary Skill in the Art

Padagis's definition of a person of ordinary skill in the art is a person having a doctoral or Master's degree in pharmaceutical sciences, a field of chemistry related to drug delivery (or a related field), with at least two years' experience developing ophthalmic compositions. Alternatively, under Padagis's definition, a person of ordinary skill in the art may have an education level lower than a doctoral degree in pharmaceutical sciences, chemistry, or a related

field if he or she commensurately has more relevant work experience.[2] Padagis's definition also permits a person of ordinary skill in the art to work as part of a multi-disciplinary team and draw upon not only his or her own skills, but also to consult with others on the team having specialized skills, to solve a given problem. Tr. 588:12–589:2.

Alcon defines a person of ordinary skill in the pertinent field as a person with an advanced degree in a pharmaceutical science or a related field and several years of experience developing, researching, and/or teaching about pharmaceutical compositions, including ophthalmic compositions. Alternatively, a person of ordinary skill in the pertinent art may possess a less advanced degree but have a greater number of years of experience. Alcon agrees with Padagis that such a person may be a member of or have access to a multi-disciplinary team including, for example, organic chemists, analytical chemists, microbiologists, and ophthalmologists and would have been able to consult with such individuals as appropriate. Tr. 300:4–23.

Each party represented that its infringement and validity positions would not change if the other party's definition of a person of ordinary skill in the art were adopted. Tr. 302:7–12, 589:7–11, 922:10–14. Because the definitions are very similar and the parties agree that resolution of the issues in this case does not change under either definition, I need not decide which definition more accurately characterizes the skill level of a person of ordinary skill in the relevant art.

IV. Infringement by Padagis's ANDA Product

At trial, the parties stipulated that Padagis's ANDA product literally meets each limitation of claim 13 of the '265 patent except for the limitation that recites "a first polyol, the first polyol being selected from mannitol, sorbitol or a combination thereof and wherein the concentration of

[2] It is not clear from Dr. Dyar's testimony whether a person could have an educational level lower than a Master's degree, or whether a person with a Master's degree would need more relevant work experience than a person with a doctoral degree.

the first polyol is at least 0.01 w/v % but no greater than 0.5 w/v %" ("first polyol limitation"). Dkt. No. 273 ¶ 1. The parties also stipulated that the product meets the additional limitations of dependent claims 14–19. *Id.* ¶ 2. Therefore, for purposes of assessing infringement, I need consider only whether Padagis's ANDA product satisfies the first polyol limitation.

Padagis submitted qualitative and quantitative information to the FDA regarding the composition of its proposed product. JTX 37 at 3 (Table P.1.1). That information did not list mannitol or sorbitol as ingredients. It did, however, list brimonidine tartrate as an ingredient. *Id.* Dr. Steven Little, Alcon's expert on pharmaceutical formulations, testified that the brimonidine tartrate in Padagis's ANDA product will dissociate into free base brimonidine and tartrate. Tr. 307:13–308:3. He explained that the dissociation results in 1.32 mg/mL of free base brimonidine and 0.68 mg/mL (or a concentration of 0.068 w/v %) of tartrate. Tr. 308:15–309:23. That testimony was undisputed. What the parties dispute is whether the tartrate in the ANDA product is equivalent to the claimed first polyol limitation and thus whether Padagis's ANDA product infringes the asserted claims under the doctrine of equivalents.

A. The Doctrine of Equivalents

The doctrine of equivalents provides a limited exception to the principle that patent infringement is determined by examining whether the accused product falls within the scope of the claim as literally written. *VLSI Tech. LLC v. Intel Corp.*, 87 F.4th 1332, 1341 (Fed. Cir. 2023). The doctrine recognizes "some non-literal scope of protection to avoid undermining the exclusivity rights authorized by Congress to incentivize certain innovations." *Id.* at 1342. The Federal Circuit has noted, however, that a finding of infringement under the doctrine of equivalents is the exception, not the rule. *NexStep, Inc. v. Comcast Cable Commc'ns, LLC*, 119 F.4th 1355, 1370–

71 (Fed. Cir. 2024); *see also Honeywell Int'l, Inc. v. Hamilton Sundstrand Corp.*, 523 F.3d 1304, 1313 (Fed. Cir. 2008).

The doctrine of equivalents asks whether "there is 'equivalence' between the elements of the accused product or process and the claimed elements of the patented invention." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 21 (1997) (citing *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 609 (1950)). A common framework used in assessing a claim of infringement under the doctrine of equivalents is known as the function-way-result test, which asks whether the accused product performs substantially the same function in substantially the same way to obtain the same result as the claimed invention. *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858, 866 (Fed. Cir. 2017). An alternative framework used to assess a claim of infringement under the doctrine of equivalents asks whether the differences between the accused product and the claimed invention are insubstantial. *Tex. Instruments Inc. v. Cypress Semiconductor Corp.*, 90 F.3d 1558, 1563–64 (Fed. Cir. 1996). Under either framework, the Supreme Court has cautioned that courts must employ "special vigilance to avoid overbroad applications of the doctrine of equivalents." *Warner-Jenkinson*, 520 U.S. at 40.

One way in which the courts have limited the doctrine of equivalents is to insist that it be applied on a limitation-by-limitation basis rather than to the invention as a whole. *Id.* at 29. Alcon argues that the threshold question here is how narrowly to define the "first polyol" limitation. Alcon seeks to parse that limitation so that the question whether Padagis's ANDA product satisfies the portion of that limitation requiring that the first polyol be "selected from mannitol, sorbitol or a combination thereof" is considered separately from the question whether Padagis's product satisfies the portion of that limitation that prescribes "wherein the concentration of the first polyol is at least 0.01 w/v % but no greater than 0.5 w/v %." Specifically, Alcon argues that Padagis's

ANDA product meets (1) the first part of the first polyol limitation under the doctrine of equivalents because tartrate is equivalent to mannitol and (2) the second part of the first polyol limitation literally because the concentration of tartrate in the ANDA product falls within the claimed range set forth in the first polyol limitation. I agree with Padagis's argument that the first polyol limitation should be evaluated as a whole and that the proper inquiry is whether tartrate at a concentration of 0.068 w/v % is equivalent to mannitol at a concentration between 0.01 and 0.5 w/v %.

The question whether the limitation should be evaluated as a whole or in two parts is relevant because the buffering capacity and anti-microbial efficacy of the first polyol (i.e., mannitol or sorbitol or a combination of the two) are concentration-dependent. *E.g.*, Tr. 554:20–555:7. Under Alcon's approach, Alcon would only need to establish that there is a concentration of mannitol (or sorbitol or a combination of the two) that provides the same buffering capacity and anti-microbial effect as tartrate at a concentration of 0.068 w/v %; it would not matter whether that concentration of mannitol fell outside the claimed concentration range for the first polyol, because the first inquiry would only be whether mannitol at any concentration is equivalent to the concentration of tartrate in Padagis's ANDA product. Under Alcon's approach, Padagis's ANDA product would therefore meet the "first polyol" claim limitation even if the concentration of mannitol needed to provide the degree of buffering and anti-microbial effect equivalent to that of tartrate at a concentration of 0.068 w/v % fell outside the claimed concentration range for mannitol in the "first polyol" limitation.

The Federal Circuit has demanded specificity of proof to establish infringement by the doctrine of equivalents in order to guard against a patentee erasing meaningful structural and functional limitations of the claim. *NexStep*, 119 F.4th at 1371. Here, assessing mannitol without

regard to its concentration would permit Alcon to erase a meaningful limit on the claim, i.e., that the claim covers the functionality of mannitol at concentrations within the range prescribed by the claim. *See* '265 patent at 3:18–23 ("[I]t would be particularly desirable to provide an ophthalmic composition, which includes borate polyol complex formed with lower concentrations of particular polyols and/or borate and includes low concentrations of BAC while exhibiting improved anti-microbial activity and desirable buffering activity."). Contrary to Alcon's contention, the concentration of the first polyol is not a free-standing limitation, but serves to define the scope of the "first polyol" limitation. For that reason, applying the doctrine of equivalents to the "first polyol" limitation requires the court to determine if the proposed substitute at the specified concentration is equivalent to mannitol or sorbitol, or a combination of the two in which the concentration of those components (not the proposed equivalent) is between 0.01 and 0.5 w/v %.

Alcon relies on the principle of claim differentiation to support its position on the proper construction of the "first polyol" limitation. It argues that claim 1 does not include a concentration range, and the fact that the concentration range is not added until claim 3 means that the limitations can be considered separately. I disagree. As a dependent claim, claim 3 is presumed to be narrower than claim 1, so while claim 1 would cover any concentration of the first polyol, the later dependent claims with concentration restrictions would cover only the specified concentration range for the first polyol. Therefore, Alcon's invocation of claim differentiation does not support its argument as to the proper analysis of the first polyol limitation.

Alcon also cites *Intendis GmbH v. Glenmark Pharms. Inc., USA*, 117 F. Supp. 3d 549 (D. Del. 2015), *aff'd*, 822 F.3d 1355 (Fed. Cir. 2016), for the proposition that the effect of the specific concentration of tartrate in Padagis's ANDA product does not need to be compared to the effect of the claimed concentration range of the first polyol. But in *Intendis*, the parties did not suggest

that the concentration mattered for the doctrine of equivalents analysis, nor did the patent discuss the roles of the specific components. *See id*. at 570–78. Therefore, the court did not need to consider the effect of the concentration range. For those reasons, *Intendis* is not instructive here.

Accordingly, I will evaluate whether tartrate at a concentration of 0.068 w/v %, as found in Padagis's ANDA product, is equivalent to mannitol, sorbitol, or a combination thereof at a concentration between 0.01 and 0.5 w/v %, as recited in the asserted claims.

B. Mannitol-Borate Interaction

Buffers are solutions that maintain their pH when acids or bases are added. They typically consist of weak conjugate acid-base pairs, which can neutralize small amounts of acids or bases that are added to a solution. Dr. William Dichtel, Padagis's expert in chemistry and, in particular, regarding the interaction of organic molecules with boron-containing compounds, explained the process by which borate and mannitol interact to increase the buffering capacity of a solution to which they are added.

Dr. Dichtel explained that a structure containing two hydroxyl (-OH) groups on adjacent carbon atoms is known as a diol. Tr. 421:5–17. Mannitol has six hydroxyl groups constituting multiple diols. Tr. 422:10–423:2. Mannitol and borate interact through those diols. Tr. 428:2–9, 429:3–17.

Because it features multiple diols, mannitol interacts more strongly with borate than compounds having only one diol (i.e., a molecule with only one pair of adjacent hydroxyl groups). Tr. 443:15–446:9, 447:13–448:6. Through its multiple diols, mannitol can interact with more than one borate molecule at the same time to form 2:1 and 3:1 borate-mannitol complexes. Tr. 450:6–454:6. When each complex is formed, one proton and one water molecule are released. Tr. 418:20–420:6, 429:18–430:6. When a 2:1 or a 3:1 borate-mannitol complex is formed, each borate

molecule releases a proton and a water molecule. A 2:1 complex therefore releases two protons, and a 3:1 complex releases three. Tr. 454:15–455:4. The release of protons is important, because the presence of free protons increases the buffering capacity of the solution. Tr. 150:9–20 (Jorgensen); Tr. 480:9–22 (Dichtel). Accordingly, the ability of mannitol to strongly interact with one or more borate ions at once greatly increases the buffering capacity of the formulation in which borate and mannitol are present. Tr. 454:15–455:4, 484:14–485:2, 490:9–22.

Dr. Dichtel's explanation of the interaction of borate with mannitol was credible and undisputed; I therefore credit it.

C. Tartrate-Borate Interaction

The parties disagree about how tartrate complexes with borate. Dr. Dichtel testified that borate can interact with molecules through either a carboxylic group (-COOH) and an adjacent hydroxyl group (-OH) or through a diol.[3] Tartrate has one diol and two carboxylic groups. Tr. 457:23–458:14. Alcon's expert in chemistry, Dr. William Jorgensen, testified that tartrate and mannitol are structurally similar because both have hydroxyl groups that form at least one diol. Based on that structural similarity and on the undisputed fact that mannitol interacts with borate through the mannitol's diols, Dr. Jorgensen concluded that borate would complex with tartrate in the same way that it complexes with mannitol, i.e., through the diol on the tartrate ion. Tr. 158:24–159:24, 164:5–165:1.

Dr. Dichtel disagreed. He relied on data reported in a journal article by Lutz et al., which compared mixtures of tartaric acid and boric acid at various pH levels. Tr. 468:4–10; DTX 324 at 1–3, Figs. 1, 2. Lutz used nuclear magnetic resonance spectroscopy to image the tartrate-borate

[3] Some witnesses referred to the -COOH structure as "carboxylate," while others referred to it as a "carboxylic group." I understand carboxylate to be the negatively charged ion from the carboxylic group; thus, the term "carboxylic group" encompasses a carboxylate. For consistency, I refer to this structure as a carboxylic group throughout this opinion.

complexes and reported the findings to show how borate and tartrate interact as a function of the pH of the solution in which they are found. Tr. 469:6–24. Dr. Dichtel explained that at high pH levels Lutz showed that borate interacts with tartrate through the diol on the tartrate ion. Tr. 474:7–18. At lower pH levels in the 6 to 8 range, however, Lutz showed that borate interacts with tartrate principally through the combination of one carboxylic group and one hydroxyl group, not through the diol on the tartrate ion. Tr. 474:19–475:14, 477:13–478:22.

Dr. Dichtel testified that the structure on which the complex forms is important because the diol structure releases a proton while the carboxylic group/hydroxyl group structure does not. Tr. 483:17–484:13. As a result, mannitol increases the buffering capacity of a formulation because it releases one or more protons when it interacts with borate. By contrast, tartrate that complexes with borate mainly through the carboxylic and hydroxyl groups is not associated with as much buffering as mannitol that complexes with borate, because a complex formed between borate and the carboxylic and hydroxyl groups does not result in the release of a proton. Tr. 483:20–485:2, 493:12–494:6.

I credit Dr. Dichtel's testimony that at a pH level between 6 and 8 the borate predominately complexes with tartrate through the carboxylic and hydroxyl groups, not through the diol on the tartrate ion. As an initial matter, Dr. Jorgenson agreed that there are multiple potential borate-tartrate complex structures. Tr. 158:24–159:24. Therefore, the dispute between the parties is not whether multiple complex structures can exist, but which structure will predominate under the relevant conditions.

Dr. Jorgenson supported his opinion that the borate-tartrate complex forms through the diol by reference to a journal article by Pizer et al. JTX 7; Tr. 160:1–160:4, 162:3–162:17. Although it is true that Pizer shows complexes formed through the diol on the tartrate ion, *see* JTX 7 at 1

(figure), Pizer's experiments were conducted at a pH of 11.5, and Pizer warned that the results reported in the article were limited to reactions at a high pH. JTX 7 at 2 ("Since this study was conducted exclusively in basic media (pH = 11.5), the results presented here are limited to those reactions which are important at high pH"); Tr. 462:1–18. Dr. Jorgensen did not offer testimony accounting for Pizer's use of a high pH, nor did he offer any explanation of how borate and tartrate would complex at a pH level between 6 and 8. Therefore, the only testimony addressing the complex that forms at a pH between 6 and 8 came from Dr. Dichtel.[4] The effect of the difference in pH between 11.5 and 6 to 8 is important because Padagis's ANDA product is formulated at pH 6.5, so the relevant pH range for Padagis's ANDA product is 6 to 8. *See* JTX 37 at 3 (stating that the pH of Padagis's ANDA product is adjusted to 6.5).

Alcon seeks to discredit Dr. Dichtel's conclusion based on his admissions regarding a prior art journal article by Van Duin et al. The Van Duin reference discusses complexing in glyceric acid, a molecule similar to tartrate, and concludes that "when the pH reaches pKa (R^o) borate esters of the a-hydroxycarboxylic acid type convert into borate esters of the diol type. With the aid of this 'charge rule' it is possible to predict the species present in solution at a certain pH." DTX 325 at 10.[5] Dr. Dichtel explained that the pKa of boric acid is 9, so the diol complex will form principally at a pH of 9 or above. Tr. 492:3–16.

[4] Alcon argues that Dr. Dichtel could have tested Padagis's ANDA product to see what complexes are found in that product. Because he did not, Alcon argues that Dr. Kabra's testimony must be credited as the only experimental evidence offered at trial. As discussed further below, Dr. Kabra's experiments do not disprove Dr. Dichtel's prediction regarding what complexes will form in Padagis's ANDA product. I find Dr. Dichtel's testimony on that issue to be credible.

[5] As Dr. Jorgensen explained, the value "pKa" is a function of the equilibrium constant for the dissociation process for an acid, which in turn is a measure of the strength of the acid. The buffering capacity of an acid is maximized when the pH of the solution and the pKa of the acid are the same. *See* Tr. 146:3–147:4.

Alcon argues that Dr. Dichtel admitted that the Van Duin reference showed an equilibrium of carboxylic/hydroxyl group complexes and diol complexes and thus that Van Duin suggests that glyceric acid and borate exhibit diol complexing under the conditions relevant for Padagis's ANDA product. Specifically, Alcon asked Dr. Dichtel about figure 8 in Van Duin. Dr. Dichtel agreed that figure 8 showed that there is an equilibrium between the hydroxyl/carboxyl group complex and the diol complex in glyceric acid, but he commented that figure 8 in Van Duin "is just a very confusing figure" that he could not "make heads or tails out of." Tr. 534:8–535:17. Dr. Dichtel concluded that the figure was inconsistent with the actual experiment that the Van Duin article described. Tr. 535:18–21.

I find that the conclusion offered by the text of the Van Duin article supports Dr. Dichtel's explanation that tartrate does not predominately complex with borate through the diol at the pH level relevant for Padagis's ANDA product, but I discount the value of that disclosure, given Dr. Dichtel's admission regarding the apparent internal inconsistencies in the Van Duin reference attributable to figure 8 in the article. Ultimately, however, I find the Van Duin reference less probative than the Lutz reference for several reasons. To begin with, Van Duin studied glyceric acid, not tartaric acid. Dr. Dichtel explained that glyceric acid and tartaric acid have similar structures, so Van Duin is "another example of how compounds that contain both a simple diol and a carboxylic acid nearby interact with boric acid at the relevant pH ranges." Tr. 486:7–21. But Van Duin did not study the molecule that is actually at issue here, so I find it less relevant than Lutz, which studied tartrate. I also ascribe less weight to Van Duin than to Lutz due to the confusion over Van Duin's findings, whereas Alcon identified no inconsistencies in Lutz's findings.[6] As a result, I give only limited weight to Van Duin, so the reference and Dr. Dichtel's

[6] I disagree with Alcon's suggestion that Dr. Dichtel's uncertainty about the import of figure 8 in Van Duin undermines the credibility of the rest of his testimony. Dr. Dichtel was a

uncertainty about figure 8 in Van Duin does not change my conclusions above, which are based on Dr. Dichtel's testimony and on the Lutz reference.

Alcon also seeks to rebut Padagis's theory that tartrate complexes with borate mainly through the carboxylic and hydroxyl groups by focusing on Dr. Dichtel's testimony that the type of complexes formed between borate and any polyol will differ at different concentrations. *E.g.*, Tr. 543:11–15. Alcon relies on that statement by Dr. Dichtel to argue that there is no basis for Padagis's assertion that borate forms a different complex with tartrate than it does with mannitol. Alcon's argument, however, flips the burden of proof on its head. Alcon bears the burden to establish infringement by a preponderance of the evidence. Alcon therefore must prove that tartrate forms the same complex as mannitol at the concentration relevant for Padagis's ANDA product; Padagis does not need to disprove that theory. Alcon did not offer evidence regarding the effect of concentration on the interaction of borate and tartrate, so the possible effect of differences in concentration does not factor into my findings.

In short, Dr. Jorgensen's testimony was directed to the types of borate-tartrate complexes that *can* form rather than focusing on the type of complexes that actually *do* form under the conditions found in Padagis's ANDA product. By contrast, Dr. Dichtel offered testimony about the type of complexes seen at the relevant pH level of the accused product, testimony that was supported by various references. I further note that Dr. Jorgensen's testimony on this issue was fairly cursory as compared to Dr. Dichtel's. Therefore, I find that at the relevant pH level of Padagis's ANDA product, tartrate interacts with borate mainly via the carboxylic and hydroxyl groups, not via the diol.

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knowledgeable and credible witness. I do not find that Dr. Dichtel's difficulty in squaring figure 8 in the Van Duin reference with the discussion in the text of the reference calls into question the remainder of his testimony, and in particular his reliance on the Lutz reference and his discussion of the Pizer reference.

D. Tartrate's Buffering Capacity

As discussed above, Dr. Dichtel explained that the way borate forms complexes is significant because it affects the formulation's buffering capacity. Specifically, he explained that at a neutral pH, borate and tartrate do not interact via the tartrate diol, and the reaction therefore does not release a proton. By contrast, borate and mannitol interact through one or more diols at a neutral pH and release one or more protons. Without the release of one or more protons, tartrate does not provide the extra buffering capacity provided by mannitol. *See* Tr. 483:20–485:2, 493:12–494:6.

Alcon does not directly challenge the details of Dr. Dichtel's explanation. Instead, Alcon points to experimental evidence that it says disproves his theory. Specifically, Alcon relies on testimony from Dr. Kabra about the experiments he ran during his development of Simbrinza® to determine the buffering capacity of the components in the Simbrinza® formulation.

Dr. Kabra explained that a composition's buffering capacity can be quantified based on the amount of sodium hydroxide (NaOH) that must be added to a solution to increase the solution's pH level. Tr. 73:20–74:16. Upon testing the Simbrinza® formulation, Dr. Kabra discovered that 19 milliliters ("mL") of NaOH per liter of Simbrinza® was required to raise the pH of Simbrinza® from 6.5 to 7.5. Tr. 75:21–76:9; PTX 109 at 9 (figure 4.1-1). He also tested a version of Simbrinza® in which boric acid was removed and found that only 11 mL of NaOH per liter of the modified formulation was required to produce the same pH increase. Tr. 80:9–81:4. Dr. Kabra attributed the difference of 8 mL between the amount of NaOH needed to produce the pH increase in the original Simbrinza® formulation and the amount needed to produce the same pH increase in the modified Simbrinza® formulation to the combined buffering effect of all the borate-polyol

complexes in Simbrinza®, since in the absence of boric acid no borate-polyol complexes could form.

Next, Dr. Kabra tested a version of Simbrinza® in which only the mannitol was removed. He found that 13.5 mL of NaOH per liter of that modified formulation was required to produce the same pH increase. Tr. 82:18–83:10. Because the difference between the 8 mL of NaOH needed to increase the pH of the original Simbrinza® without borate and the 13.5 mL of NaOH needed to increase the pH of the Simbrinza® formulation without mannitol was 5.5 mL, he attributed that difference to the buffering effect of the borate-mannitol complexes in Simbrinza®. That left a gap of 2.5 mL of NaOH between the buffering effect of the borate-polyol complexes as a whole and the effect of the borate-mannitol complexes, i.e., 5.5 subtracted from 8. Dr. Kabra attributed that 2.5 mL of NaOH to the borate-tartrate complexes formed with the tartrate derived from the brimonidine tartrate found in Simbrinza®. Tr. 124:6–125:4. Based on Dr. Kabra's testimony, Alcon argues that the mannitol in Simbrinza® contributes only slightly more buffering than the tartrate in Padagis's ANDA product and that the formulation of the ANDA product is therefore equivalent to Simbrinza® and to the formulation recited in claim 13 of the '265 patent.

I reject Alcon's theory. The biggest flaw with the theory is that Dr. Kabra assumed that borate buffers only when it is complexed with mannitol or tartrate. In reality, when Dr. Kabra measured the buffering capacity of the Simbrinza® formulation, he was measuring the sum of the buffering capacities of borate, mannitol, tartrate, borate-tartrate complexes, and borate-mannitol complexes. Similarly, when he removed the mannitol and measured the buffering capacity, he was measuring the sum of the buffering capacities of borate, tartrate, and borate-tartrate complexes. But when performing his calculations, Dr. Kabra incorrectly assumed (1) that the buffering capacity measured in the Simbrinza® formulation was attributable only to the buffering

capacities of borate-tartrate complexes and borate-mannitol complexes and (2) that the buffering capacity measured in the Simbrinza® formulation without mannitol was attributable only to the buffering capacity of borate-tartrate complexes. Based on those assumptions, he attributed the difference between the buffering capacity of the Simbrinza® formulation without borate and the Simbrinza® without mannitol (2.5 mL of NaOH) entirely to the borate-tartrate complex. But there was evidence at trial that uncomplexed borate has its own non-negligible buffering capacity. *E.g.*, JTX 59 at 1:23–24; '265 patent at 2:65–3:12; Tr. 646:5–24. Accordingly, some portion of the calculated 2.5 mL of NaOH needed to be attributed to borate and some to the borate-tartrate complexes. But because Dr. Kabra never measured tartrate alone, his experiments did not show how much buffering capacity was contributed by the borate-tartrate complexes as opposed to borate by itself.

That evidentiary gap is fatal to Alcon's doctrine of equivalents theory. Alcon's theory is that the buffering effect of mannitol varies based on its concentration, so a concentration of mannitol at the low end of the range recited in claim 13 of the '265 patent would result in a buffering effect equivalent to the buffering effect of the tartrate in Padagis's ANDA product. The problem with that theory is that, as discussed, Dr. Kabra's experiments do not establish how much, if any, buffering capacity is attributable to tartrate. Therefore, Alcon's assumption that there is some concentration of mannitol within the claimed range that provides the same amount of buffering capacity as the tartrate provides in Padagis's ANDA product is entirely speculative. To the contrary, Dr. Dichtel's testimony suggests that the amount of buffering capacity provided by tartrate is very low at the pH of Padagis's ANDA product compared to the buffering capacity provided by mannitol. *See* Tr. 446:6–9 (estimating that mannitol is a stronger complexing agent with boron than simple diols by "three orders of magnitude"), 483:2–485:2, 490:9–22, 493:12–

494:11, 499:15–500:2. 500:21–502:6. That suggests that even at a concentration of 0.01 w/v %, the minimum concentration of mannitol permitted by the claims (which is about 15% of the concentration of tartrate in Padagis's ANDA product), mannitol could contribute more buffering capacity than the amount of buffering capacity contributed by the tartrate found in Padagis's product.

In addition to Dr. Kabra's testimony regarding his experiments, Alcon seeks to rely on admissions from Dr. Dichtel to prove its theory. Specifically, Alcon argues that Dr. Dichtel conceded that the buffering effect of a low concentration of mannitol would be the same as the buffering effect of tartrate in Padagis's ANDA product. I disagree with Alcon's characterization of that testimony. Dr. Dichtel merely acknowledged that he did not know what effect adding a small concentration of mannitol would have on Padagis's ANDA product. Tr. 564:13–18. Dr. Dichtel's inability to identify the effect of such a change in the ANDA product does not establish that there is a mannitol concentration within the claimed range that provides so little change in buffering capacity that it is effectively the same as a formulation containing tartrate instead of mannitol. If Alcon wished to base its theory of infringement on that proposition, it was required to prove it, which it did not.[7]

Focusing on Dr. Kabra's conclusion regarding the difference between the buffering effect of mannitol (5.5 mL of NaOH) and the buffering effect of tartrate (2.5 mL of NaOh), Alcon argues that Dr. Kabra's testing demonstrates that the borate-tartrate complexes in Padagis's ANDA product impact buffering "to nearly the same extent as the borate-mannitol complexes in

[7] Alcon argues in its opening brief that the tartrate in Padagis's ANDA product has a "measurable effect" on the buffering of the composition. Dkt. No. 280 at 20. But that assertion merely underscores the problem with Alcon's infringement theory, which is that although the effect of tartrate on the buffering of the claimed composition was "measurable," Alcon did not directly measure it, or at least failed to offer evidence of any such measurement.

Simbrinza®," Dkt. No. 280 at 3, and that "[t]o the extent that the tartrate has a somewhat lesser effect on buffering than mannitol, this is merely a difference of degree, not a difference of kind," *id.* at 19. But even on its face, the assertion that a difference of 3 mL of NaOH is inconsequential is simply attorney argument.[8] Moreover, there are two factual problems with Alcon's argument.

First, there was testimony that mannitol's buffering capacity is concentration-dependent. There was no testimony explaining how to compare the concentrations of mannitol in Simbrinza® and tartrate in the modified Simbrinza® formulation (which Alcon characterizes as identical to Padagis's ANDA product). And there was no testimony explaining whether the results of Dr. Kabra's experiments needed to be scaled (and no testimony of how to do so) to account for any difference in concentration levels for mannitol and tartrate. Second, Dr. Kabra measured Simbrinza®'s buffering effect as 19 mL of NaOH. Even assuming that his calculation is correct that the difference between the buffering effect of mannitol and tartrate is 3 mL of NaOH, there was no evidence at trial suggesting that 3 mL of NaOH is inconsequential on a scale of 0 to 19 (i.e., the measured buffering capacity of the unmodified Simbrinza® formulation).[9]

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[8] In support of its contention that any difference in buffering effect between Padagis's ANDA product and the claimed formation was only "a difference of degree, not of kind," Alcon cites the Federal Circuit's opinion in *Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp.*, 149 F.3d 1309, 1321 (Fed. Cir. 1998). But in that case, the court overturned a summary judgment of noninfringement on the ground that the difference between the claimed structure and the accused product was "very slight" and "subtle," and that the dispute in the record over the substantiality of the difference raised "genuine issues of material fact as to equivalence, issues that must be resolved by the finder of fact." In this case, the issue of equivalence is presented to me, as the finder of fact, and in light of the dimension of the differences, I find that the accused ANDA product is not equivalent to the claimed formulation.

[9] Padagis challenges the accuracy of Dr. Kabra's calculation of the buffering effect of Padagis's ANDA product, based on Alcon's assertion in its proposed pretrial order that one of Alcon's experts had measured that effect as requiring 11.32 mL of NaOH to raise the pH of the solution from 6.5 to 7.5, which differs significantly from the 13.5 mL of NaOH derived by Dr. Kabra for the Simbrinza® formulation with the mannitol removed. Dkt. No. 241-2 at ¶¶ 54–56. While that factual assertion is the pretrial order is binding on Alcon, *see Amgen Inc. v. Conn. Ret. Plans & Trust Funds*, 568 U.S. 455, 471 (2013) (citing with approval *Am. Title Ins. Co . v. Lacelaw*

Alcon faults Padagis for not offering evidence to rebut Dr. Kabra's testimony about his experiments and declining to cross-examine Dr. Kabra on that topic. But it was Alcon's burden to prove that Dr. Kabra's experiments with modified Simbrinza® formulations help prove that Padagis's ANDA product infringes the asserted claims, and I do not find that Dr. Kabra's testing evidence advances Alcon's case.[10]

In sum, Dr. Kabra's testing evidence is fundamentally flawed because his tests did not measure the effect of the tartrate in Simbrinza® directly, but only inferred that effect by excluding the effect of mannitol on the buffering of the Simbrinza® formulation. Not only is that inference inconsistent with the evidence at trial (namely, that borate has a buffering capacity even when it is uncomplexed), but no expert offered testimony on Alcon's behalf explaining this theory.[11] As noted above, there are significant gaps in Alcon's theory that, given the high level of ordinary skill

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Corp. 861 F.2d 224, 226 (9th Cir. 1988)), it is not necessary to resolve that challenge to Dr. Kabra's calculations, since I find that those calculations, even if accepted as true, do not support Alcon's infringement claims.

[10] Alcon argues that criticisms of Dr. Kabra's testimony by Padagis's attorneys are entitled to no weight. But Alcon bears the burden of proof on this issue. Therefore, the "criticisms," which are actually identifications of evidentiary holes in Alcon's theory, go to the question whether Alcon has met its burden of proof, and it is entirely appropriate to consider them for that purpose.

[11] Alcon states in its post-trial brief that Dr. Kabra offered testimony about "a formulation with the same components as Padagis's ANDA product," and that "the borate-tartrate complexes in Padagis's ANDA Product impact buffering in the same way and to nearly the same extent as the borate-mannitol complexes in Simbrinza." But Dr. Kabra did not test Padagis's ANDA product itself, so presumably Alcon means Simbrinza® with the mannitol removed when it references "Padagis's ANDA product." Dkt. No. 280 at 2–3. In any event, testimony from Dr. Kabra about Padagis's ANDA product would be improper expert testimony. *See Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1361 (Fed. Cir. 2008). Although Dr. Kabra can appropriately testify as a fact witness about his own experiments, including the design and results of those experiments, any testimony directed to whether the tartrate in Padagis's ANDA product offers the same buffering capacity increase as the claimed first polyol is not appropriate subject matter for a fact witness. *See HVLPO2, LLC v. Oxygen Frog, LLC*, 949 F.3d 685, 689 (Fed. Cir. 2020) ("The prohibition of unqualified witness testimony extends to the ultimate conclusions of infringement . . . as well as to the underlying technical questions.").

for the art, I cannot fill without the aid of testimony from an expert. Accordingly, I find that Alcon has not proved by a preponderance of the evidence that the borate-tartrate complexes formed in Padagis's ANDA product produce the same or substantially the same increase in buffering capacity as the claimed mannitol-borate complexes.

E. Tartrate's Anti-Microbial Activity

Dr. George Zhanel, Alcon's expert on microbiology, testified that borate-tartrate complexes have anti-microbial activity. Tr. 225:15–21, 227:9–19. But Dr. Zhanel did no testing of his own; instead, he based his testimony about anti-microbial activity of the polyols on the diol structures identified by Dr. Jorgensen. Dr. Zhanel's testimony was thus predicated on the assumption that at neutral pH levels the tartrate in Padagis's ANDA product complexes with borate on tartrate's diol structure, not on tartrate's carboxylic/hydroxyl group structure. As discussed above, however, the evidence at trial showed that assumption to be incorrect.

Dr. Zhanel did not analyze the anti-microbial activity of any structure other than the diol structures. *See* Tr. 211:9–15, 212:24–213:12, 219:12–220:1. His testimony therefore does not establish that the borate-tartrate complexes that form under the relevant conditions have anti-microbial activity equivalent to the anti-microbial activity that is attributable to the diol complexes generated by borate-mannitol interactions.

Alcon seeks to fill that evidentiary gap with an admission by Dr. Dichtel that he did not know whether the difference in the structure of the borate complexes with mannitol and tartrate would make a difference in anti-microbial activity. *See* Tr. 538:1–15. But again, Dr. Dichtel's inability to disprove Alcon's infringement theory does not discharge Alcon's burden of proof with regard to that theory.

Alcon also seeks to fill the evidentiary gap in Dr. Zhanel's theory with the preservative efficacy testing ("PET") data that Padagis submitted with its ANDA. Dr. Zhanel testified that Padagis's PET data showed that Padagis's ANDA product eradicated contamination. He concluded from the data that the tartrate must be supplementing the anti-microbial activity of the BAC in the formulation because the low level of BAC in Padagis's ANDA product would be unable to achieve the PET data results without help. Tr. 228:8–19, 232:11–24. Dr. Zhanel, however, admitted that the PET data is reported only in pass/fail format, and that the PET data measures the results for the complete ANDA product as opposed to measuring results on a component-by-component basis. Tr. 243:13–244:11. He also admitted that he did not compare Padagis's ANDA product with tartrate to the same product without tartrate. Tr. 250:16–251:8. And finally, he admitted that he did not review any microbiological data comparing the efficacy of the borate-tartrate complex to that of the mannitol-borate complex. Tr. 254:6–14. The absence of evidence of that sort undermines the significance of the PET data as support for Alcon's theory of equivalency.

Padagis points to testing reported by Alcon to rebut Dr. Zhanel's conclusions. The specification describes an example composition, Composition S, that lacks mannitol, sorbitol, and tartrate. '265 patent at Table I (Composition S). That composition, despite lacking both a first polyol and tartrate, passed all four PET standards. Tr. 271:6–10; *see also* Tr. 607:5–608:18 (describing Composition S testing recorded in an Alcon laboratory notebook, DTX 998 at 67). Those test results cast doubt on Dr. Zhanel's hypothesis that a formulation with a low concentration of BAC could not pass the PET standards without the help of tartrate.[12]

[12] Dr. Zhanel sought to reconcile the conflict between the test results and his opinion by explaining that Composition S has a lower osmolality than the ANDA product, creating an inhospitable environment for microbes, which affected the PET results. Tr. 270:14–24. But Dr. Zhanel admitted that the osmolality range identified as desirable in the patent is 200 to 400

Taking all these evidentiary gaps together, I find that Alcon has not proved by a preponderance of the evidence that the tartrate in Padagis's ANDA product produces the same enhanced anti-microbial activity as the mannitol and tartrate in the claimed formulation.

F. Function-Way-Result

As discussed above, I find that the mannitol and borate in the claimed composition interact via the diol or diols on the mannitol molecule, while the borate and tartrate in Padagis's ANDA product interact principally via the carboxylic and hydroxyl groups. That difference matters for purposes of both the buffering effect of the first polyol in the formulation and the anti-microbial effect of the first polyol.

As noted, the evidence showed that the borate-mannitol complexing on the diol structures in the claimed composition will release one or more protons, which enhances the buffering effect of the formulation, while the borate-tartrate complexing on the carboxylic/hydroxyl group structure in Padagis's ANDA product does not release a proton, and thus does not enhance the buffering effect of the formulation. And Alcon's evidence that the first polyol in the claimed composition has anti-microbial effects depends on the complexing between borate and the first polyol taking place on the diol structures of the first polyol, something that does not occur to a significant degree in the borate-tartrate interactions found in Padagis's ANDA product at the relevant pH levels. Alcon has therefore failed to show that the tartrate in Padagis's ANDA product enhances the anti-microbial effect of the formulation. Accordingly, I find that the tartrate in

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milliosmoles per kilogram and range identified as preferable is 240 to 360 milliosmoles per kilogram. Tr. 274:21–275:3. He further admitted that the osmolality level for Composition S is 237 milliosmoles per kilogram, placing the osmolality level for Composition S within the acceptable range and only 3 milliosmoles short of the preferable range. Tr. 275:5–16. Moreover, Dr. Zhanel admitted that he did not do any testing to determine the effect of osmolality on the microbial activity for Composition S. Tr. 275:18–22. Based on this record, I give little weight to Dr. Zhanel's osmolality explanation for the conflict between the test results and his opinion.

Padagis's ANDA product functions in a different way than the mannitol in the claimed composition does and fails to achieve the same results.

Alcon argues that the patent does not require any particular type of first polyol complexing. Therefore, Alcon argues, requiring borate and tartrate to complex with the same structure as borate and mannitol would be too narrow an approach to evaluating the doctrine of equivalents. Alcon cites *Abraxis Bioscience, Inc. v. Mayne Pharma (USA) Inc.*, 467 F.3d 1370, 1380 (Fed. Cir. 2006), and *Intendis GMBH v. Glenmark Pharms. Ltd.*, 117 F. Supp. 3d 549, 576 (D. Del. 2015), to support that proposition. But as the Federal Circuit explained in *Abraxis*, "[w]hat constitutes equivalency must be determined against the context of the patent, the prior art, and the particular circumstances of the case." 467 F.3d at 1380 (citing *Graver Tank*, 339 U.S. at 609).

Here, even though the asserted claims do not require a particular type of complexing, the parties agree that (1) one purpose of the first polyol is to increase buffering capacity, (2) another purpose of the first polyol is to enhance the anti-microbial effect of the BAC, (3) mannitol increases buffering capacity by releasing one or more protons, and (4) the anti-microbial effect of mannitol is attributable to the borate-mannitol complexing on the diol structures of the mannitol molecule. Alcon does not dispute Padagis's evidence that tartrate can complex with borate in multiple different ways and that only some of those ways involve the release of a proton. Accordingly, the facts of this case and the way in which the parties have litigated this case give rise to a narrower inquiry into the "way" prong of the function-way-result analysis than was called for by the facts of *Abraxis* or *Intendis*. *See Abraxis*, 467 F.3d at 1380 (the question was whether "metal ion chelation" occurred, not which specific ions were chelated); *Intendis*, 117 F. Supp. 3d at 576 (record evidence showed all the excipients at issue functioned in substantially the same way).

I also find that the tartrate in Padagis's ANDA product produces a different result than the mannitol in the claimed composition. The tartrate does not release a proton when it interacts with the borate, whereas the mannitol does. As a result, tartrate does not produce substantially the same increase in buffering capacity as mannitol. Alcon also did not prove that tartrate has the same anti-microbial effect as mannitol, because Dr. Zhanel based his opinions regarding that issue on a complex structure that does not form in Padagis's ANDA product at relevant pH levels.

In sum, Alcon has not proved that the tartrate in Padagis's ANDA product functions in substantially the same way or that it produces substantially the same results as the mannitol recited in the asserted claims.[13]

G. Insubstantial Differences

In the alternative, Alcon argues that the tartrate in Padagis's ANDA product is equivalent to the first polyol in the asserted claims under the "insubstantial differences" test for equivalency. In support of that theory, Alcon again relies on the testimony by Dr. Jorgensen and Dr. Zhanel that the structural similarities between mannitol and tartrate would allow both of those molecules to form complexes with borate and therefore contribute similarly to the anti-microbial activity of the compositions as well as contribute to the buffering capacity of the compositions.

What Alcon's argument overlooks is that although tartrate provides some of the same functionality as mannitol, it does so through a different chemical process. As discussed above, that difference in the chemical processes leading to the formation of complexes with borate is significant because it affects the degree of buffering and anti-microbial efficacy contributed by an amount of tartrate similar to the amount of the first polyol used in the patented formulation. For

[13] The parties spent little time addressing the "function" of tartrate in the Padagis ANDA product. Because the "way" and "result" of the tartrate-based reaction found in that product are different from the "way" and "result" of the mannitol-based reaction found in the claimed composition, it is not necessary to consider the "function" prong of the "function-way-result" test.

the same reasons that the difference leads to the conclusion that the two formulations are not equivalent under the function-way-result test, the difference cannot be regarded as insubstantial under the insubstantial differences test.

In passing, citing JTX 30 at 1, Alcon argues that Padagis admitted in its ANDA filing that its ANDA product is "equivalent in formulation" to Simbrinza®. Dkt. No. 280 at 21. But that statement was made as part of Padagis's presentation in support of its argument to the FDA that the formulation of its ANDA product is bioequivalent to Simbrinza®. That is not the same as stating that Padagis's ANDA product is equivalent to the patented composition for purposes of the doctrine of equivalents. The en banc Federal Circuit made that point explicitly in *Abbott Laboratories v. Sandoz, Inc.*, 566 F.3d 1282, 1298 (Fed. Cir. 2009), where the court wrote:

> While bioequivalency may be relevant to the function prong of the function-way-result test, bioequivalency and equivalent infringement are different inquiries. Bioequivalency is a regulatory and medical concern aimed at establishing that two compounds are effectively the same for pharmaceutical purposes. In contrast, equivalency for purposes of patent infringement requires an element-by-element comparison of the patent claim and the accused product, requiring not only equivalent function but also equivalent way and result. Different attributes of a given product may thus be relevant to bioequivalency but not equivalent infringement, and vice versa.

See also The Johns Hopkins Univ. v. Datascope Corp., 543 F.3d 1342, 1349 n.3 (Fed. Cir. 2008) ("FDA equivalence is irrelevant to patent law because it involves fundamentally different inquiries."). Alcon's theory of equivalence fares no better under the "insubstantial differences" test than under the "function-way-result" test.

In sum, Alcon has not proved by a preponderance of the evidence that Padagis's ANDA product meets the "first polyol" limitation under the doctrine of equivalents and therefore has not shown that Padagis's ANDA product infringes the asserted claims. Because I have found that the tartrate found in Padagis's ANDA product does not satisfy the "first polyol" limitation of the

asserted claims under the doctrine of equivalents, I need not address Padagis's arguments for noninfringement based on the alternative grounds under the doctrines of ensnarement or disclosure dedication.

V. Obviousness of the Asserted Claims

As a defense and counterclaim, Padagis contends that the asserted claims of the '265 patent are invalid for obviousness. Obviousness under 35 U.S.C. § 103 is a question of law based on underlying findings of fact. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The underlying factual considerations "include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations" bearing on obviousness. *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 736 (Fed. Cir. 2013) (citing *Graham*, 383 U.S. at 17–18, and *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007)). "The obviousness analysis should not be conducted 'in a narrow, rigid manner,' but should instead focus on whether a claimed invention is merely 'the result [] of ordinary innovation,' which is not entitled to patent protection." *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 595 (D. Del. 2018) (quoting *KSR*, 550 U.S. at 427–28), *aff'd sub nom*. *Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184 (Fed. Cir. 2019).

An obviousness determination "requires finding that a person of ordinary skill in the art would have been motivated to combine or modify the teachings in the prior art and would have had a reasonable expectation of success in doing so." *Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341, 1347 (Fed. Cir. 2024) (quoting *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1382 (Fed. Cir. 2019), and *Regents of Univ. of Cal. v. Broad Inst., Inc.*, 903 F.3d 1286, 1291 (Fed. Cir. 2018)). The party in a district court proceeding challenging the validity of issued claims bears the burden

of proving that the asserted claims would have been obvious and must do so by clear and convincing evidence. *See Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014).

Padagis asserts that each limitation other than the concentration of BAC is disclosed in one or more of three principal prior art references. Those references are (1) U.S. Patent Application Publication No. US 2008/0095863 ("Kabra"), JTX 58, which was published on April 24, 2008; (2) U.S. Patent No. 5,505,953 ("Chowhan"), JTX 59, which issued on April 9, 1996; and (3) U.S. Patent No. 6,316,441 ("Dean"), JTX 67, which issued on November 13, 2001. It is undisputed that all three references are prior art to the '265 patent. [14] Padagis further argues that a person of ordinary skill in the art would have been motivated to combine the pertinent components from each of those references and decrease the BAC concentration to the level recited in the claims, and that such a person would have had a reasonable expectation of success in doing so.

Alcon does not dispute that each limitation except for the BAC concentration can be found in at least one of the three cited references. But Alcon argues that Padagis has not shown, by clear and convincing evidence, that a person of ordinary skill in the art (1) would have been motivated to reduce the concentration of BAC to as low as 0.0035 w/v %, which was below the level disclosed in any of the pertinent prior art; (2) would have been motivated to combine the remaining limitations, taken from various prior art references, in the way the asserted claims do; and (3) would have had a reasonable expectation of success by so doing.

During trial, Alcon agreed that claims 13 and 16–19 rise or fall together for purposes of the invalidity analysis. Dkt. No. 273 ¶ 4. For present purposes, I will focus on the question whether claim 13 would have been obvious. I address claims 14 and 15 later.

[14] The '265 patent has a priority date of June 19, 2009.

A. Padagis's Obviousness Evidence

As discussed below, all but one of the limitations in claim 13 of the '265 patent can be found in the Kabra reference, the Chowhan reference, and/or the Dean reference. That remaining limitation is the concentration of BAC in the composition, which the claim recites must be "greater than 0.00001 w/v % but less than 0.0035 w/v %." Alcon argues that it would not have been obvious to use BAC at the concentration levels set forth in the claim. Alcon also argues that a person of ordinary skill in the art would not have picked out various limitations from Kabra, Chowhan, and Dean to arrive at the claimed composition.

1. Evidence Regarding Composition Components

Kabra and Chowhan are both addressed to anti-microbial ophthalmic compositions. *E.g.*, Chowhan at 1:14–18; Kabra ¶ 2. Dean is addressed to the use of brinzolamide and brimonidine as the active ingredients in such compositions, with BAC serving as the anti-microbial agent. Dean at 1:8–12. Kabra explicitly contemplates a multi-dose ophthalmic composition, Kabra ¶ 3–4, and discusses the difficulty of formulating a preservative with a concentration of an anti-microbial agent high enough to be effective, yet low enough to minimize any toxic side-effects, *id.* ¶ 5.

Both Kabra and Chowhan recognize that the use of BAC as a preservative is widely known in the art and that BAC can be used in conjunction with multiple polyols to enhance the efficacy of the BAC. *E.g.*, Kabra ¶ 6; Chowhan at 1:44–46. Both references also state that borate buffer systems in combination with one or more polyols, such as mannitol, can enhance the anti-microbial activity of a preservative while achieving and maintaining a desired pH level in the formulation. Kabra ¶ 7 ("Borate buffer systems in combination with one or more polyols, such as mannitol, aid the anti-microbial activity . . . ."); Chowhan at 1:14–25 ("[B]orate-polyol complexes in ophthalmic compositions . . . are useful as buffers and/or antimicrobial agents . . . ."), 2:5–6 ("borate-polyol

complexes are formed by mixing boric acid and/or its salts with polyols"), 1:64–2:4, 2:13–17, 2:57–60. Chowhan suggests using mannitol, sorbitol, propylene glycol, and/or glycerine as a polyol in such a formulation, *id.* at 2:50–54, and specifically identifies using mannitol and propylene glycol together in one formulation, *id*. at 7:11–24 (example 5). These references thus disclose the combination of BAC, borate, and two polyols (namely, mannitol and propylene glycol) in a multi-dose ophthalmic composition.

Chowhan further discloses that borate-polyol complexes have greater anti-microbial activity than typical borate buffers and that they increase the anti-microbial efficacy of other anti-microbial agents when used in combination with those agents. *Id*. at Abstract. Like Kabra, Chowhan suggests that BAC can be used in conjunction with one or more polyols to enhance the efficacy of the BAC. Chowhan at 1:64–2:4, 2:55–60. Kabra and Chowhan also disclose the use of water in their example formulations. Kabra at Tables 2–9; Chowhan at Examples 4–12. And Chowhan discloses two formulations in which BAC is the only preservative. Chowhan at 4:58–14 (Formulation 9), 5:44–64 (Formulation 10); Tr. 664:13–18.

Kabra and Chowhan further disclose that a viscosity-enhancing agent can be added to their compositions, and both identify a carboxyvinyl polymer (sometimes referred to as "carbomer" and sometimes referred to by its trade name, Carbopol®) as an appropriate viscosity-enhancing agent. Kabra ¶¶ 47, 54; Chowhan at 3:13–17; '265 patent at 9:2–4. Kabra further discloses that its compositions can be used in all types of topically administrable compositions, including solutions and suspensions, and it notes that compositions are typically administered by applying drops of a solution or suspension to the eye one to four times a day. Kabra ¶ 57. Based on Kabra's suggestion to use carboxyvinyl polymer as a thickening, viscosity-enhancing, or stability-enhancing agent in its formulation, which can be prepared as a suspension, *id*. ¶ 54, I find that Kabra discloses a

composition in the form of a suspension containing a therapeutic agent, with carbomer as a suspending agent. *See* Tr. 671:1–17 (explaining that viscosity is important because a person of ordinary skill in the art would want the active ingredient particles to remain suspended for an extended period of time to satisfy commercial needs). Finally, Kabra identifies brinzolamide and brimonidine and their combination as potential active ingredients, Kabra ¶ 35, and Dean discloses a formulation containing brinzolamide and brimonidine tartrate as the active ingredients, mannitol as a polyol, carbomer as the suspending agent, and BAC as the preservative, Dean at 5:60–7:58 (Examples 6–9).

Alcon argues that Padagis's obviousness theory improperly picks and chooses various claimed limitations from the Kabra, Chowhan, and Dean references. I disagree. I find that a person of ordinary skill in the art seeking to formulate a multi-dose ophthalmic composition would be aware that BAC was widely used as a preservative in ophthalmic compositions and was well known for having excellent anti-microbial properties, as explained in both Kabra and Chowhan. Kabra ¶ 6; Chowhan at 1:44–49. Such a person would also know, as Kabra and Chowhan explain, that BAC at high concentrations has toxic side-effects for the eye.

Kabra recognizes that lowering the concentration of BAC in an ophthalmic composition would reduce BAC's toxic side-effects, but could fail to provide sufficient anti-microbial efficacy. Kabra ¶ 5. And both Kabra and Chowhan propose the same solution to that problem, which is to formulate a composition with a lower BAC concentration, while maintaining efficacy by combining the BAC with a borate-polyol complex. Kabra ¶ 7; Chowhan at 1:64–2:4, 2:13–17.

Chowhan touts the benefits of that approach, explaining that borate-polyol complexes can be used with known preservatives, such as BAC, to meet preservative efficacy and disinfection standards. *Id.* at 2:55–60; *see also id.* at 1:64–2:4 (Borate-polyol complexes "unexpectedly

increase the anti-microbial efficacy of other anti-microbial agents when used in combination."), 4:25–5:65 (examples 2 and 3, formulations 9 and 10).

Given that Kabra and Chowhan identify the same problem and recommend the same solution, I find that a person of ordinary skill in the art looking to develop a formulation according to Kabra would readily find in Kabra and Chowhan the suggestion to combine BAC with borate and one or more polyols. This is not a case in which the patent challenger is picking particular limitations from an assortment of references. Rather, the references are largely overlapping, and each of the components of the composition recited in claim 13 of the '265 patent is conspicuously present in at least one of the three references on which Padagis principally relies.

Alcon argues that Chowhan and Kabra both teach away from using BAC as the preservative. Again, I disagree. Alcon is correct that both references acknowledge that BAC has drawbacks. *See* Kabra ¶ 6; Chowhan at 1:45–50. But I do not find that either reference teaches away from using BAC. "[A] reference does not teach away if it merely expresses a general preference for an alternative invention but does not criticize, discredit or otherwise discourage investigation into the invention claimed." *UCB, Inc. v. Actavis Lab'ys UT, Inc.*, 65 F.4th 679, 692 (Fed. Cir. 2023) (citation omitted). Here, both references suggest a way to overcome BAC's drawbacks by enhancing its effectiveness so that it can be used at lower, less toxic concentrations. Kabra ¶ 6; Chowhan at 2:13–22. That suggestion is not buried in the details of Kabra and Chowhan, but is a principal point of both references and counsels in favor of finding a motivation to continue to use BAC as a preservative but at a lower concentration. *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("a given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine").

The conclusion that BAC was known to be a highly effective preservative, but one presenting certain challenges for a formulator is further supported by the disclosures in the '265 patent's specification regarding the state of the art in this field. The specification states that it "has been found that BAC is often desirable as a preservative," but that "[i]t has also been found . . . that BAC can rapidly lose its anti-microbial efficacy when its concentration falls below certain threshold levels. This loss of efficacy is quite unfortunate since concentrations of BAC below these threshold levels can exhibit significantly lower toxicological effects." '265 patent at 2:32–40. The specification adds that it "is generally known that borate-polyol complexes can be used in ophthalmic compositions to enhance anti-microbial activity in the presence of a preservative . . . [and it] has also been shown that increase in amounts of polyol such as sorbitol or mannitol can significantly increase anti-microbial activity even when relatively low amounts of borate are employed." *Id*. at 2:53–61. Those statements in the specification of the '265 patent constitute admissions by the patentee as to the state of the prior art and the general knowledge of persons of skill in the art prior to the application. *See PharmaStem Therapeutics, Inc. v. ViaCell*, *Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007) ("Admissions in the specification regarding the prior art are binding on the patentee for purposes of a later inquiry into obviousness.").

2. Evidence Regarding Component Concentrations

Having found that all the components recited in claim 13 are present in the prior art, I next consider whether the references disclose that those components are present in the claimed amounts or concentrations recited in the claim. Beginning with the first and second polyols and borate, Chowhan suggests a range of molar ratios of borate to polyol. Chowhan at 2:60–62. Chowhan also suggests weight percentages for the borate-polyol structure. *Id*. at 3:3–8. Chowhan qualified those suggestions by stating that the optimum amounts will depend on the particular product in

which those components are used, and that the optimum amounts can readily be determined by a person of ordinary skill in the art. *Id*. at 3:8–12.

Dr. Craig Dyar, Padagis's expert on drug delivery technology, including for ophthalmic compositions, testified that he performed calculations using Chowhan's molar ratios and weight percentages to determine the corresponding concentration ranges. He then compared the concentration ranges calculated from Chowhan to the concentration ranges recited in the asserted claims in order to determine whether the ranges overlapped; he found that the ranges do overlap. Tr. 650:7–654:12. Dr. Little did not disagree with the accuracy of Dr. Dyar's calculations. *E.g.*, Tr. 955:6–11. Therefore, I find that Chowhan discloses the claimed concentrations of borate and the polyols.

The more difficult question is whether, in view of the prior art, it would have been obvious for a person of ordinary skill in the art to select a concentration of BAC as low as 0.0035 w/v %, the upper limit of the concentration range recited in the asserted claims. Padagis acknowledges that no reference discusses or suggests using BAC at such a low concentration. However, Padagis argues that the 0.004 w/v % concentration of BAC disclosed in Chowhan is close enough to 0.0035 w/v % that a person of ordinary skill in the art would be motivated to decrease the BAC concentration slightly to 0.0035 w/v % in light of the well-recognized desirability of minimizing the concentration of BAC.

Alcon does not dispute that a person of ordinary skill would be motivated to reduce the concentration of BAC. Instead, Alcon argues that the issue is not whether a person of ordinary skill would reduce the concentration of BAC from 0.004 w/v % to 0.0035 w/v % to reach the upper limit of the claimed range, because a person of ordinary skill would not start with a concentration of 0.004 w/v %. Alcon contends that the evidence shows that a person of ordinary skill would

start with a higher concentration, such as 0.01 w/v %, and that the person would not be motivated to try to reduce the concentration of BAC from 0.01 to 0.0035 w/v %, a reduction in concentration of approximately two-thirds. Alcon further contends that even if a person of ordinary skill in the art would be motivated to reduce the concentration of BAC in a suspension to a level as low as 0.0035 w/v %, Padagis has not shown that such a person would have a reasonable expectation of success with such a low concentration of BAC.

There are two problems with Padagis's argument that a person of skill in the art would start with a BAC concentration of 0.004 w/v % and would be motivated to reduce the BAC concentration to the slightly lower level of 0.0035 w/v %. First, the only references in Chowhan to the 0.004% w/v % concentration level of BAC are in examples 1 and 2 in the specification, each of which lists BAC at that concentration level as a component of one of the formulations. But there is no indication in Chowhan that the BAC in those two formulations was effective as an anti-microbial agent. As Alcon pointed out at trial, there was no efficacy data of any type reported for those formulations in Chowhan. *See* Tr. 943:12–944:2, 711:7–10. Besides those two examples, BAC was added to only one other example in Chowhan. The concentration of BAC in that example, however, was 0.01 w/v %, not 0.004 w/v %. Chowhan at 8:31–9:14 (example 10).

The second problem with Padagis's reliance on Chowhan as the starting point for a concentration of BAC at the 0.004 w/v % level is that the Chowhan reference is addressed to solutions, while the asserted claims of the '265 patent are addressed to suspensions. *Compare* '265 patent at 19:34 ("wherein the composition is a suspension") *with* Chowhan at 2:7–12 ("The resultant solution may then be used as a buffer and/or antimicrobial agent . . . ."), 5:35–37, 8:33–35.[15] Therefore, Alcon argues, a person of ordinary skill in the art would not use the examples

[15] To confirm that the examples in Chowhan are solutions, Alcon relies on testimony from Dr. Dyar on cross-examination. When he was questioned about the Chowhan examples, Dr. Dyar

from the solutions in Chowhan as a starting point when optimizing the contents of the suspensions—namely the BAC—claimed in the '265 patent.

Dr. Kabra and Dr. Little explained that there is a difference in the effectiveness of BAC in suspensions as opposed to solutions because suspensions are formulated with viscosity-enhancing agents such as the carboxyvinyl polymer used in the claimed suspensions. Tr. 924:4–8. Dr. Kabra and Dr. Little explained that such suspending agents are negatively charged, and they interact with the positively charged BAC. *See* Tr. 52:3–53:21 918:17–919:11, 920:20–921:3. That interaction, Dr. Little testified, reduces the efficacy of the BAC in the formulation, so a person of ordinary skill would expect that more BAC would be needed in a suspension than in a solution to achieve the same anti-microbial effect in a suspension as in a solution. Tr. 924:8–925:8. Dr. Kabra acknowledged that the interaction between the BAC and the carboxyvinyl polymer that serves as a viscosity-enhancing agent significantly reduces the antimicrobial effectiveness of the BAC; he estimated the reduction in that efficacy as being "about half." *See* Tr. 61:20–62:9.

The testimony from Dr. Kabra and Dr. Little on that issue is consistent with the fact that the lowest concentration of BAC shown by the prior art for a suspension that was addressed at trial was 0.01 w/v %, *see, e.g.*, Tr. 37:3–9, which is slightly more than twice the 0.004 w/v % concentration used in Chowhan's solutions. Padagis offered no contrary evidence on this point

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was asked, "Neither of those formulations is a suspension; isn't that right?" He responded, "I don't know that for a fact . . . unless it states." Tr. 699:5–9. When pressed as to whether he had checked to determine whether those formulations were suspensions, he responded, "I didn't check that. I detailed from the formulation." Tr. 699:12–15. Counsel for Alcon then showed Dr. Dyar a passage in Chowhan that discusses the preparation of the relevant formulations and refers to a "solution" rather than a suspension. Dr. Dyar responded, "Yes, I see that from there." Tr. 699:17–700:3. Padagis does not identify any evidence suggesting that the relevant examples in Chowhan are suspensions. Dr. Little also testified that Chowhan's formulations containing 0.004 w/v % of BAC are solutions, not suspensions. Tr. 941:4–13.

about the charge interaction. Accordingly, I find that the 0.004 w/v % concentration level of BAC in examples 1 and 2 of Chowhan cannot be assumed to be transferable to suspensions.

For that reason, Padagis's burden is to show that a person of ordinary skill would expect success with a concentration of 0.0035 w/v %, when the closest prior art uses a BAC concentration approximately three times that high, at 0.01 w/v %. Padagis has not met that burden. Padagis relies on Dr. Dyar's testimony that it would have been a matter of "routine optimization" for a person of ordinary skill in the art to reduce the concentration of BAC to 0.0035 w/v % and his explanation that such a person would be motivated to do so because formulators are always trying to minimize the concentration of the ingredients in a formulation in order to reduce the risk of side-effects. Tr. 656:3–19. But Dr. Dyar's testimony was based on his assumption that the starting point for such an exercise would be the 0.004 w/v % concentration set forth in the two examples in Chowhan. *See* Tr. 663:23–64:8. Dr. Dyar did not testify that a person of ordinary skill would have been motivated to reduce the BAC concentration from 0.01 w/v % to 0.0035 w/v % nor that such a person would have expected to have success when making such a large reduction in concentration of BAC.

In sum, I find that Padagis has not proved by clear and convincing evidence that a person of ordinary skill in the art would have been motivated to formulate a preservative composition with a BAC concentration below 0.01 w/v % and would have had a reasonable expectation of success in doing so.

3. Claims 14 and 15

Claim 14 adds the following limitation to claim 13: "the resistance provided by the composition to normalization of tear pH after instillation in the eye is less than 15 µl of 1 M NaOH/mL of composition." Claim 15 adds the following limitation to claim 13: "the viscosity of

the suspension is greater than 20 cps but less than 500 cps with the viscosity of the suspension being measured at a high shear rate of 120 sec-1 at room temperature." If, as I have held, claim 13 is not invalid for obviousness, then neither are claims 14 and 15, which depend from claim 13. *See Ortho-McNeil Pharm., Inc. v. Mylan Lab'ys, Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008); *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992); *Hartness Int'l, Inc. v. Simplimatic Eng'g Co.,* 819 F.2d 1100, 1108 (Fed. Cir. 1987); *In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988) ("Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious.").

B. Objective Considerations

Alcon argues that evidence as to several objective considerations confirms that Padagis has failed to satisfy its burden of proof on the issue of obviousness. Specifically, Alcon points to evidence of (1) a purported long-felt, unmet need for the patented inventions; (2) the unexpected results achieved by those inventions; and (3) the success experienced by the commercial embodiment of the inventions. Upon analysis of each of those factors, I find that they provide some moderate support for Alcon's contention that the inventions were non-obvious.

1. Long-Felt, Unmet Need

"Evidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer the need would not have persisted had the solution been obvious." *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1056 (Fed. Cir. 2016) (en banc). Alcon's expert on clinical ophthalmology and the treatment of glaucoma, Dr. Robert Fechtner, testified that BAC has been used for a long time at concentrations between 0.004 w/v % and 0.01 w/v % to prevent contamination, but that it was known to have dose-dependent toxicity. Tr. 789:21–790:12, 788:7–22. He explained that given the widely recognized concerns about the

toxicity of BAC at high concentrations, ophthalmologists have been advocating since about 2000 for compositions with lower BAC concentrations. Tr. 797:20–798:5. Despite the recognized desire among practitioners for compositions with lower BAC concentrations, Dr. Fechtner noted that manufacturers had failed to produce new compositions with lower BAC concentrations until Alcon released Simbrinza®. Tr. 804:5–805:1, 806:2–7, 809:4–23.

However, Dr. Fechtner admitted that even today there remains a need for ophthalmic products with lower levels of BAC. Tr. 826:17–21. Therefore, Simbrinza® did not fully satisfy the perceived need to decrease the concentration sufficiently to fill the unmet need. For that reason, while this factor weighs somewhat in Alcon's favor, it is not a compelling consideration supporting Alcon's argument of non-obviousness.

2. Unexpected Results

In a bid to show that Alcon's patented invention produced unexpected results, Alcon relies on Dr. Kabra's testimony that he did not expect his test formulation with lower levels of BAC and two polyols to pass the preservative efficacy standards and was surprised when the patented formulation did so. But Dr. Kabra was the inventor and thus an interested party. His testimony on the issue of unexpected results would have been more persuasive if it had been backed up by evidence that others in the field had the same reaction to Dr. Kabra's invention. But Alcon did not offer any evidence from others supporting Dr. Kabra's claim of surprise, such as articles or third-party testimony.

Although I do not doubt that Dr. Kabra was excited and even surprised at the results he obtained with his two-polyol preservative formulation, his reaction as evidence of unexpected results must be discounted in view of his status as the inventor and the absence of any evidence of similar reactions from disinterested parties. *See Forest Lab'ys, LLC v. Sigmapharm Lab'ys*, LLC,

918 F.3d 928, 937 (Fed. Cir. 2019) (unexpected results consideration asks whether the patented invention exhibits a superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected); *cf. Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 968 (Fed. Cir. 2014) (Inventor testimony should be treated with skepticism due to the inventor's self-interest in obtaining or maintaining an existing patent.). Alcon's unexpected results evidence is therefore not entitled to great weight.

3. Commercial Success

Evidence that the patented invention has been a commercial success tends to rebut the obviousness of the invention; that proposition is based on the presumption that a successful product would have been brought to market earlier if it had been obvious. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). In order to take advantage of that presumption, however, the patentee must also prove that the commercial success of the product is linked to the patented invention as opposed to unclaimed features or circumstances. *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008).

Alcon presented evidence that approximately seven million units of Simbrinza® have been sold, resulting in revenue of approximately $460 million since 2013. Tr. 842:17–843:1. Dr. Michal Malkiewicz, Alcon's expert on economic analysis as it pertains to commercial success, testified that Simbrinza®'s net revenue and sales volume have trended upward since the product launched, which is indicative of a successful product. Tr. 844:7–17. He added that this trend was especially noteworthy in view of the challenges that Simbrinza® has faced, including having to pause its field force promotion efforts in 2019 and the increasing market activity of competing generic products. Tr. 852:9–853:1. Padagis's expert on economics and the analysis of commercial

success, Dr. DeForest McDuff, disagreed with Dr. Malkiewicz's interpretation of the sales data. Tr. 1099:1–12.

I need not resolve the competing expert opinions over what the sales and revenue data show, because Alcon did not establish a firm nexus between the alleged commercial success and the claimed invention. Dr. Fechtner testified that he prescribes Simbrinza® for two reasons: (1) its low BAC concentration and (2) the high efficacy provided by the fixed combination of two "excellent" active ingredients, brinzolamide and brimonidine. Tr. 809:15–810:6. But he admitted that he still prescribes drugs for treating glaucoma that contain 0.01 w/v % BAC when he decides that medication is the right medication for the particular patient. Tr. 826:2–16. And Dr. Malkiewicz admitted that he was unaware of any marketing communications for Simbrinza® stating that it contains a low level of BAC. Tr. 878:24–879:20.

Beyond that, the active ingredients in Simbrinza® are covered by the Dean patent, not the asserted patent, which does not identify the therapeutic agent or agents at all. Thus, there is no convincing proof of a nexus between the commercial success attributable to Simbrinza®'s efficacy and the claims asserted in this case. Dr. Malkiewicz did not apportion the commercial success between the efficacy of the active ingredients in Simbrinza® and its low BAC concentration; rather, as he admitted, he presumed that a nexus existed. Tr. 881:9–882:5. This failure to link commercial success to the specific novel features of the patented invention undermines the probative force of Alcon's evidence. *See Asyst*, 544 F.3d at 1316 (Fed. Cir. 2008).

The second reason I need not resolve the battle of the experts is that financial success is not significantly probative of non-obviousness when potential competitors are faced with a blocking patent. *Merck*, 395 F.3d at 1377. A patent is considered to be a blocking patent if a

competitor's practice of a later patent would infringe that earlier patent. *Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 903 F.3d 1310, 1337 (Fed. Cir. 2018).

Here, the prior art Dean patent, which is owned by Alcon, claims the use of brinzolamide and brimonidine for treating glaucoma. Tr. 638:6–10. Dean therefore claims Simbrinza®'s coadministration of its two active ingredients, as confirmed by Simbrinza®'s label. *See* DTX 1171 at 16. Dr. Dyar explained that a potential competitor would have been deterred from developing a formulation similar to Simbrinza® because the competitor could not administer brinzolamide and brimonidine together without risking infringement of the Dean patent. Tr. 1077:20–1078:3.

Alcon's only response to Padagis's blocking-patent argument is that Simbrinza® has a second indication, ocular hypertension, and a competitor could have pursued the composition by carving out the glaucoma indication. Dr. Fechtner explained that ocular hypertension means that the pressure in the eye is elevated. Tr. 771:7–11. He further explained that ocular hypertension is a prominent risk factor for developing glaucoma. Tr. 771:14–15. But he admitted that there is "no razor sharp dividing line" between ocular hypertension and glaucoma; rather, once prolonged hypertension causes damage to the eye, a diagnosis of glaucoma is given. Tr. 771:20–772:3. In other words, ocular hypertension is not a distinct disease from glaucoma such that glaucoma could be easily carved out of the label. Indeed, Simbrinza®'s label notes that Simbrinza® is indicated for "the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension." DTX 1171 at 5. Given that the condition of ocular hypertension cannot easily be disentangled from the disease of glaucoma, I do not find compelling Alcon's argument that a competitor could carve out the glaucoma indication and focus only on the ocular hypertension indication to avoid the risk of infringing the Dean patent. In addition, I find that Alcon's argument about focusing on treating ocular hypertension rather than glaucoma is undercut

by Alcon's economics expert, who referred only to the "glaucoma market" rather than attempting to separate that market from the "ocular hypertension market," thereby suggesting those markets are one and the same. Alcon offered no other evidence to rebut Padagis's blocking patent argument, so I find the "blocking" effect of the Dean patent significantly undercuts Alcon's commercial success claims.

As a whole, I do not find that the objective considerations weigh strongly in Alcon's favor. I find that the objective considerations of unexpected results and commercial success have modest force at best. And while I find that the objective consideration of a long-felt unmet need weighs somewhat in Alcon's favor and therefore provides some support for Alcon's contention that the asserted claims are not invalid for obviousness, Alcon's evidence for that factor is not particularly compelling. Therefore, the objective considerations do not play a major role in my analysis of the issue of obviousness. What is clear, however, is that the objective considerations do not buttress Padagis's obviousness case.

VI. Enablement of Asserted Claims

In addition to obviousness, Padagis argues that the asserted claims of the '265 patent are invalid for failing to enable the claimed invention. Section 112 of the Patent Act requires that the patent's specification must enable a person of ordinary skill in the art to make and use the claimed invention. The enablement requirement "enforces the essential 'quid pro quo' of the patent bargain by requiring a patentee to teach the public how 'to practice the full scope of the claimed invention.'" *McRo, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1099–1100 (Fed. Cir. 2020) (quoting *AK Steel Corp. v. Sollac*, 344 F3d 1234, 1244 (Fed. Cir. 2003)). "A claim is not enabled if (as it is the challenger's burden to prove by clear and convincing evidence) a relevant artisan would not be able to practice the claimed invention 'without undue experimentation.'" *Pac.*

Biosciences of Cal., Inc. v. Oxford Nanoport Techs., Inc., 996 F.3d 1342, 1350 (Fed. Cir. 2021) (quoting *Amgen Inc v. Sanofi*, 987 F.3d 1080, 1084 (Fed. Cir. 2021)). The enablement requirement guards against "overbroad claiming that might otherwise attempt to cover more than was actually invented. Thus, a patentee chooses broad claim language at the peril of losing any claim that cannot be enabled across its full scope of coverage." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012).

Padagis's non-enablement theory is based on the assumption that the claimed composition must meet a particular efficacy requirement. Padagis explains that although the claims recite a BAC concentration range between 0.00001 w/v % and 0.0035 w/v %, the lowest BAC concentration disclosed by the specification is 0.001 w/v %, which is 100 times lower than the lowest BAC concentration used in any example in the '265 patent. *See* Tr. 674:11–676:16. Padagis contends that the claims are not enabled for a BAC concentration of less than 0.001 w/v % because neither the specification nor the prior art provides any guidance on making the claimed product with a concentration of BAC as low as 0.00001 w/v % while retaining its efficacy. *See* Tr. 676:7–16 (Dr. Dyar testifying that "if that [i.e., BAC at a concentration of 0.00001 w/v %] worked, that would be like, I don't know what word to put with it because I don't have any expectation that that would work at that low of a level"); Tr. 677:7–18 ("Q: Would a person of ordinary skill in the art know whether the lower end of the claimed BAC concentration range . . . would work as a preservative in an ophthalmic composition? A: . . . Not based on anything that you've seen here or in the prior art or my experience.").[16] Because a claim must be enabled across

[16] In addition to Dr. Dyar's testimony, Padagis relies on Alcon's evidence that suspensions formed with viscosity-enhancing agents such as carboxyvinyl polymers require higher BAC concentrations to overcome the negative charge associated with those polymers. Padagis also points to testimony from Dr. Kabra that he was surprised that test formulations with BAC at a concentration of 0.002 w/v % and 0.003 w/v % passed all the conventional standards, Tr. 56:13–58:11; testimony from Dr. Zhanel that he did not expect BAC to have substantial anti-microbial

the full scope of the claim in order for the claim to be valid, Padagis argues that the asserted claims of the '265 patent are invalid for lack of enablement.

Nothing in the claims, however, requires the formulation to meet a particular level of efficacy, such as the United States and European standards for anti-microbial formulations. Padagis may be correct that a composition with a BAC concentration at the low end of the claimed range would have such a limited anti-microbial effect that it could not be successfully marketed. But Padagis has not argued that it would require undue experimentation to put the claimed components into a formulation at amounts within the claimed ranges, and Padagis did not offer evidence at trial that BAC would cease to have any anti-microbial effect at a very low concentration. It is therefore reasonable to conclude that BAC has some anti-microbial effect at the low end of the claimed concentration range, even though that anti-microbial effect may not be sufficient to satisfy the needs of a commercial product. *See CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338–39 (Fed. Cir. 2003). For that reason, Padagis has not met its burden of showing by clear and convincing evidence that the claims are not enabled across the full range of BAC concentrations set forth in the claims. *See Alcon Rsch. Ltd. v. Barr Lab'ys, Inc.*, 745 F.3d 1180, 1189 (Fed. Cir. 2014) (finding that the defendant failed to prove the claims were not enabled when the "claims as a whole merely require that the addition of PECO to the composition provide some increase in chemical stability, but do not require a particular level of stability or a particular magnitude of increase").

effects at a concentration below 0.003 w/v %, Tr. 235:19–236:11; and testimony from Dr. Little that a person of ordinary skill in the art would not have assumed such a composition would work without the need for test results demonstrating that it would be effective, Tr. 943:12–944:4.

VII. Conclusion

With respect to Alcon's allegations of infringement, I conclude that Alcon has not proved by a preponderance of the evidence that Padagis's ANDA product infringes claims 13–19 of the '265 patent. With respect to Padagis's allegations of invalidity, I conclude that Padagis has not proved by clear and convincing evidence that claims 13–19 are invalid for obviousness under 35 U.S.C. § 103. I also conclude that Padagis has not proved by clear and convincing evidence that claims 13–19 are invalid for the lack of enablement under 35 U.S.C. § 112.

The parties are directed to file a proposed form of judgment in accordance with these Findings of Fact and Conclusions of Law within five days of the issuance of this order.

* * * * *

The briefs that Alcon submitted in support of its proposed findings of fact and conclusions of law in this case were both submitted under seal. For that reason, I have filed this opinion under seal. Within ten business days of the issuance of this order, Alcon is directed to advise the court by letter whether any portions of this order should remain under seal, and if so which portions. Any request that portions of the order 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 5th day of February, 2025.

William C. Bryson

WILLIAM C. BRYSON
UNITED STATES CIRCUIT JUDGE