UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC
Petitioner

v.

ALCON RESEARCH, LTD.
Patent Owner

Patent No. 8,268,299
Issue Date: September 18, 2012
Title: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

Inter Partes Review No. IPR2017-01053

PETITION FOR *INTER PARTES* REVIEW
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 *ET SEQ.*

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1017	The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, 13th Ed., (2001), Merck Research Laboratories, 5767, 8797, 9842.
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1029	Save up to $20 on your next four prescriptions with this card, March 27, 2010, http://web.archive.org/web/20100327064125/http://www.travatanz.com
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Argentum Pharmaceuticals, LLC ("**Petitioner**") petitions for *Inter Partes* Review (IPR), seeking cancellation of claims 1-28 ("**challenged claims**") of U.S. Patent No. 8,268,299 to Kabra *et al*. ("**the '299 patent**"; Ex. 1001), which is owned by Alcon Research, Ltd. Concurrently filed herewith is a Power of Attorney pursuant to 37 CFR §42.10(b). The required fee set forth in 37 CFR §42.15(a) has been paid on-line. The Office is authorized to charge any additional fees required or credit any overpayments to Deposit Account No. 19-0741.

I. MANDATORY NOTICES (37 C.F.R. § 42.8)

A. Real Parties-In-Interest under 37 C.F.R. § 42.8(b)(1)

Argentum Pharmaceuticals LLC; Intelligent Pharma Research LLC; APS GP LLC; APS GP Investors LLC; and KVK-TECH, Inc.

B. Related Matters under 37 C.F.R. § 42.8(b)(2)

The '299 patent has been the subject of the following proceedings: *Alcon Research Ltd. v. Mylan Pharmacuticals, Inc.*, 1:13-cv-01332; *Alcon Research Ltd. v.Wockhardt Ltd.*, 1:13-cv-02040; *Alcon Research Ltd. v. Micro Labs Ltd.*, 1:14-cv-00014; *Alcon Research Ltd. v. Watson Laboratories, Inc.*, 1:14-cv-00647; *Alcon Research Ltd. v. Akorn, Inc.*, 1:15-cv-00479; *Alcon Research Ltd. v. Lupin Ltd.*, 1:15-cv-00621; *Apotex Corp. v. Alcon Research, Ltd.*, IPR2013-00428, settled 7/21/2014 (Paper 60). Petitioner was not a party to any of these cases.

C. Lead and Backup Counsel

Lead Counsel	Backup Counsel	Backup Counsel
Michael R. Houston, Ph.D. Reg. No. 58,486 Foley & Lardner LLP	Joseph P. Meara, Ph.D. Reg. No. 44,932 James P. McParland, Ph.D. Reg. No. 69,440 Foley & Lardner LLP	Tyler C. Liu Reg. No. 72,126 Argentum Pharmaceuticals LLC

D. Service Information

Foley & Lardner LLP, 3000 K St. NW, Suite 600, Washington, DC. 20008. Petitioner consents to service by email at: ARG-travatanZ@foley.com.

II. GROUNDS FOR STANDING

Petitioner certifies under 37 C.F.R. §42.104(a) that the '299 patent is available for IPR and that Petitioner is not barred or estopped from requesting an IPR challenging the claims on the grounds identified in this petition.

III. IDENTIFICATION OF CHALLENGE

Per 37 C.F.R. §42.104(b) Petitioner requests cancellation of claims 1-28 of the '299 patent on the following grounds (pre-AIA):

Ground	References	Claims
1. Obviousness	Xia in view of Schneider and Chowhan	1, 2, 4-8, 16, 17, 20
2. Obviousness	Xia in view of Schneider, the Travatan® Label, and Chowhan	28

3. Obviousness	Xia in view of Schneider, Chowhan, and Gadd	1-23, 25-26
4. Obviousness	Xia in view of Schneider, the Travatan® Label, Chowhan, and Gadd	24 and 27-28

In support of the proposed grounds, this Petition is accompanied by the declarations of Dr. Erning Xia (Ex. 1002) and Dr. Yvonne Buys (Ex. 1021).

IV. THRESHOLD REQUIREMENT FOR INTER PARTES REVIEW

A Petitioner for *inter partes* review must demonstrate "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. §314(a). This Petition meets that threshold. For each of the grounds of unpatentability proposed below, there is a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims. Indeed, the Board has previously instituted trial against the '299 patent on some of the very same art in IPR2013-00428, and should do so again here.

V. SUMMARY OF ARGUMENTS

The ophthalmic compositions recited in the claims of the '299 patent are simply an obvious repackaging of well-known components from prior art ophthalmic compositions in an attempt to evergreen a patent family. The uses and properties of the components claimed in the '299 patent were recognized as of the earliest possible priority date of the patent. Alcon obtained the '299 patent by drafting claims that purport to be complicated – reciting specific ranges of

concentrations for ingredients, and alleged properties of the claimed composition. But the claims of the ’299 patent recite subject matter that was both simple and obvious as of the filing date of the ’299 patent. All of the ranges of concentrations and properties recited in the claims were known in the prior art.

The ’299 patent purports to be founded on the alleged discovery that ions interfere with the antimicrobial activity of zinc. But this phenomenon was known for at least 30 years before the earliest possible priority date of the patent. The claims also recite that the claimed ophthalmic compositions satisfy standardized pharmacopeia tests. But these tests were satisfied by compositions having the claimed components well before the filing date of the ’299 patent.

In sum, the claims of the ’299 patent recite ophthalmic compositions containing known components used for their known functions and having entirely expected properties. Further, a person of ordinary skill in the art (“POSA”) would have had a reasonable expectation of success in preparing the claimed compositions using known techniques. As Petitioner is reasonably likely to prevail in showing obviousness over the prior art, inter partes review of the ’299 patent should be instituted.

VI. CLAIM CONSTRUCTION

Under 37 C.F.R. § 42.100(b), the challenged claims must be given their broadest reasonable interpretations (“BRI”) in light of the patent specification as

understood by a POSA. The Board has previously construed the following claim terms exactly as presented here and should do so again. *See Apotex Corp. v. Alcon Research, Ltd.*, IPR2013-00428, Paper 9, 5-6.

The BRI of the claim term "**zinc ions at a concentration of"** encompasses the concentration of zinc salts used to prepare the claimed composition. As shown in the specification of the '299 patent, the concentration of zinc ions in the claimed compositions is equal to the concentration of zinc salt added to form the composition. *See* Ex. 1001, 4:41-53. Complete dissociation of zinc salts into zinc ions is presumed in aqueous compositions at relevant salt concentrations because zinc salts are highly soluble in water. Ex. 1002 ¶¶22-23.

Claims 24 and 28 recite concentrations of "**zinc chloride ionized**," and claim 27 recites a concentration of "ionized zinc chloride." These terms are not used in the specification of the '299 patent and were not explicitly defined during prosecution of the '299 patent. As zinc chloride is not ionized in ophthalmic compositions, the BRI for "zinc chloride ionized" and "ionized zinc chloride" encompasses the concentration of zinc chloride added. Ex. 1002 ¶24.

The BRI of the claim term "**polyol**," as used in the '299 patent, encompasses "any compound having at least one hydroxyl group on each of two adjacent carbon atoms that are not in trans configuration relative to each other." Ex. 1001, 6:19-

28; Ex. 1002 ¶¶25-26.

Based on disclosure in the ’299 patent specification Ex. 1001, 3:27-29), a POSA would have understood that “**self-preserved ophthalmic composition”** as used in the claims of the ’299 patent refers to ophthalmic compositions that do not contain a conventional antimicrobial preservative, such as benzalkonium chloride (“BAC”), polyquaternium-1, chlorite, or hydrogen peroxide. Ex. 1002, ¶27. This meaning is identical to the Board’s previous claim construction of this term. *Apotex*, IPR2013-00428, Paper 9, 6.

The specification of the ’299 patent does not define the term “**anionic species**.” However, based on the use of the term in the ’299 patent, a POSA would have understood that "anionic species" refers to negatively charged ions. Generally, in aqueous solutions, ions are the result of dissolution of ionic compounds, such as salts. Thus, the BRI of “anionic species” encompasses any element or molecule that is negatively charged in solution. Ex. 1002 ¶¶28, 31.

The specification of the ’299 patent states that “‘substantially free of multivalent buffering anions’ means that the composition either does not contain any multivalent buffering anions or contains an amount of said anions that does not inhibit the ability of the composition to satisfy specified preservative efficacy standards (*e.g.*, USP, EP or JP).” Ex. 1001, 5:22-27. Therefore, the BRI for the claim term "**does not contain**" multivalent buffering anions or metal cations

other than zinc encompasses a composition containing multivalent buffering anions or metal cations other than zinc, so long as the composition also meets specified preservative efficacy standards. Ex. 1002 ¶¶29-30.

All other terms of all challenged claims are presumed to take on their ordinary and customary meanings.

VII. PERSON OF SKILL IN THE ART

A POSA is presumed to be aware of all pertinent art and is a person of ordinary creativity. As of 2006, such a POSA would have had knowledge of the scientific literature concerning antimicrobial preservation, strategies for inhibiting microbial growth and the development of ophthalmic formulations, including knowledge of a wide array of excipients suitable for use in ophthalmic formulations and their properties. A POSA as of 2006 would typically have (*i*) a Ph.D. in microbiology or chemistry (or a related field) with at least a few years of experience in the development of ophthalmic formulations, or (*ii*) a BS or MS in microbiology or chemistry (or a related field) with significant practical experience (5 or more years) in the development of ophthalmic formulations. A POSA may work as part of a multi-disciplinary team and draw upon not only his or her own skills, but also take advantage of certain specialized skills of others in the team, to solve a given problem. For example, a microbiologist, a chemist and a physician may be part of the team. Ex. 1002 ¶¶15-17.

As evidenced by the references described herein, at least as of September 21, 2006, the earliest possible priority date ("EPPD") of the '299 patent, the subject matter claimed in claims 1-28 was well known to a POSA.

VIII. CLAIM-BY-CLAIM EXPLANATION OF GROUNDS FOR UNPATENTABILITY

Claims 1-28 are unpatentable as shown in the detailed grounds for unpatentability below.

A. Ground 1: Claims 1, 2, 4-8, 16, 17 and 20 Would Have Been Obvious Over Xia in view of Schneider and Chowhan

Claims 1, 2, 4-8, 16, 17 and 20 would have been obvious over the combination of Xia, Schneider, and Chowhan. WO 2005/097067 to Xia (Ex. 1003), titled "Zinc Preservative Composition and Method of Use" was published on October 20, 2005. Xia claims priority to U.S. Appl. No. 10/812,543, filed March 29, 2004 and qualifies as prior art to the '299 patent under 35 U.S.C. §102(a) and (e). The "Schneider" reference, U.S. Patent No. 6,011,062 (Ex. 1007), issued on January 4, 2000, and is titled "Storage-stable prostaglandin compositions." The Chowhan reference, U.S Patent No. 6,143,799 (Ex. 1004), titled "Use of Borate-Polyol Complexes in Ophthalmic Compositions," issued November 7, 2000. Thus, Schneider and Chowhan each published more than one year before the EPPD of the '299 patent and therefore qualify as prior art to the '299 patent under §102(b), pre-AIA.

As shown in the following claim chart and discussed below, the cited references teach or suggest all of the claimed limitations, and a POSA would have arrived at the compositions of the claims using only routine experimentation. "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, (CCPA 1955); *see In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). Further, the concentration ranges disclosed in Xia, Schneider and Chowhan overlap the claimed ranges of concentrations, establishing a *prima facie* case of obviousness. *See Peterson*, 315 F.3d at 1330.

'299 patent	**Disclosures of Xia, Schneider and Chowhan**
Claim 1. A multi-dose, self-preserved ophthalmic composition, comprising:	"The present invention relates to a composition that includes a **preservative-effective amount** of a soluble zinc compound …. According to one embodiment, the composition is an **ophthalmic solution**… In one embodiment, the composition is an eyedrop solution." Ex. 1003, 3. "Most preferred are compositions prepared for topical administration to the eye" such as Formulation A. Ex. 1007, 7:7-9; 9:21-42. "The **ophthalmic compositions** of the present invention comprise borate-polyol complexes." Ex. 1004, 2:4 -12.

'299 patent	**Disclosures of Xia, Schneider and Chowhan**
zinc ions at a concentration of 0.04 to 0.4 mM; and	"Preferably, the zinc compound is selected from the group comprising zinc citrate and zinc chloride. . . ." Ex. 1003, 5. "the composition has a minimum of about 0.001 wt.%[1] [**0.074 mM $ZnCl_2$**][2], about 0.005 wt.% [**0.37 mM $ZnCl_2$**], about 0.01 wt.% or about 0.05 wt.% of a zinc compound per total weight of the composition and/or a maximum of about 1 wt.%, about 0.5 wt.%, about 0.1 wt.% or about 0.05 wt.% of the zinc compound per total weight of the composition." Ex. 1003, 5.
borate and polyol, the borate being present in the composition at a concentration of 0.1 to 2.0% w/v and	Example 2 of Schneider discloses Formulation A, containing **0.3% w/v boric acid** and a **polyol**—mannitol. Ex. 1007, 9:21-42. Examples 2 and 3 in Xia contain **0.850 wt.% boric acid and 0.090 wt.% sodium borate**. Ex. 1003, 17-18. "[C]omfort agents such as … **propylene glycol** can also be added." Ex. 1003, 14. "Preferred polyols are … **propylene glycol** and **sorbitol**." Ex. 1004, 3:4-6.

[1] As admitted by Alcon during prosecution of the '299 patent, the wt.% (%w/w) is approximately equal to the % w/v for purposes of the claims. Ex. 1008, 365.

[2] The formula for conversion of w/v% (or wt%) to molarity is (w/v% / molar mass) × 10, and is routine in the art. Ex. 1002 ¶¶46, 50.

’299 patent	Disclosures of Xia, Schneider and Chowhan
the polyol being present in the composition at a concentration of 0.25 to 2.5% w/v,	“Examples of suitable agents which may be utilized to adjust the tonicity or osmolality of the formulations include … **mannitol**, dextrose, glycerine, and **propylene glycol**. Ex. 1003. 7:21-25.
the polyol comprising propylene glycol in the composition at a concentration of 0.25 to 1.25% w/v and	“The borate-polyol complexes are utilized in the compositions of the present invention in an amount between **about 0.5 to about 6.0 percent** by weight (wt %), preferably between **about 1.0 to about 2.5 wt %**.” Ex. 1004, 3:44-47.
sorbitol in the composition at a concentration of 0.05 to 0.5% w/v; wherein	At the minimum concentrations claimed, the composition of claim 1 comprises **0.4% w/v borate-polyol** (0.1% w/v borate + 0.25% w/v propylene glycol + 0.05% w/v sorbitol.
	At the maximum concentrations claimed, the composition of claim 1 comprises **3.75% w/v borate-polyol** (2.0% w/v borate + 1.25% w/v of propylene glycol + 0.5% w/v sorbitol.
	“The molar ratio of borate to polyol is generally **between about 1:0.1 to 1:10**, and preferably between about 1:0.25 and about 1:2.5.” Ex. 1004, 3:15-34.
	At the minimum borate and polyol concentrations claimed, the composition of claim 1 comprises 0.1% w/v borate [16 mM borate] to 0.3% w/v total polyol (0.25% w/v propylene glycol + 0.05% w/v sorbitol) [36 mM polyol]. **The borate to polyol molar ratio in this case is 1:2.2.**
	At the maximum borate and polyol concentrations claimed, the composition of claim 1 comprises 2.0% borate [330 mM borate] to 1.75% w/v polyol (1.25% w/v propylene glycol + 0.5% w/v sorbitol) [194 mM polyol]. **The borate to polyol molar ratio in this case is 1:0.6.**

'299 patent	**Disclosures of Xia, Schneider and Chowhan**
(i) the composition has a concentration of anionic species less than 15 mM; and	"The aqueous solutions of the present invention **are typically adjusted** with tonicity agents to approximate the tonicity of normal lacrimal fluids (approximately equivalent to a 0.9 wt.% solution of sodium chloride **or 2.8 wt.% glycerol solution**). Ex. 1003, 10. "phosphate [an anion] is a good buffer but, when used in concentrations generally found in ophthalmic formulations, **it reduces the antimicrobial activity of preservatives**." Ex. 1004, 1:45-48.
(ii) the composition exhibits sufficient antimicrobial activity to allow the composition to satisfy USP 27 preservative efficacy requirements.	Xia teaches a composition that includes a preservative-effective amount of a soluble zinc compound. Ex. 1003, 3. "Based on the acceptance criteria for bacteria or fungus a solution is acceptable if the number of viable **bacteria or fungus recovered per ml is reduced by at least 3.0 logs at day 14** and after the rechallenge at day 14, the **concentration of bacteria or fungus is reduced by at least 3.0 logs by day 28**." Ex. 1003, 15. These test requirements are more stringent than the USP 27 requirements, explained below. "The following general procedure was used for evaluating the preservative efficacy (PE) of various eye drop solutions against *Staphylococcus aureus* (ATCC 6538), *Eschrechia* [sic] *coli* (ATCC 8739), *Pseudomonas aeruginosa* (ATCC 9027), *Candida albicans* (ATCC 10231) and *Aspergillus niger* (ATCC 16404)…" Ex. 1003, 14. These are the five organisms tested in the USP 27. Ex. 1014, 2002-2004. "An organism challenge approach based on the **British Pharmacopoeia** ("BP") 1988 Test for Efficacy of Preservatives in Pharmaceutical Products was used to evaluate the antimicrobial preservative efficacy of Formulations C and D." Ex. 1004, 9:38-41.

Claims 1 & 4-6: Claim 1 is directed to a multi-dose, self-preserved

ophthalmic composition containing zinc ions, borate, and polyol (propylene glycol and sorbitol) at various concentrations and meeting a concentration limit on anionic species and a preservative efficacy requirement. Claim 4 depends from claim 1, and adds an effective amount of a therapeutic agent to the composition. Claim 5 depends from claim 1 and recites that the composition further comprises a therapeutic agent selected from the group consisting of bimatoprost, latanoprost, travoprost and unoprostone. Claim 6 depends from claim 5 and recites that the therapeutic agent comprises travoprost. Because a POSA would have been motivated to combine Xia, Schneider and Chowhan as described below, and because these references disclose each of the claimed components within the claimed concentration ranges, as well as meeting the other claim requirements and teaching how to make such formulations, claims 1 and 4-6 would have been obvious.

Xia discloses that traditional preservatives used in multi-dose, ophthalmic compositions can cause irritation and discomfort. To remedy that problem, Xia provides self-preserved multi-dose ophthalmic compositions comprising zinc ions (at the claimed concentrations), a therapeutic agent (which alone meets the limitation of claim 4 (Ex. 1002 ¶¶67-68)), borate and propylene glycol (which is a polyol). Ex. 1003, 2-3, 12, 14. The compositions employ less than a preservative-effective amount of a primary preservative agent and preferably have no primary

preservative agent. *Id.*, 3-4, 9. Among the therapeutic agents disclosed by Xia are glaucoma agents such as prostaglandins. *Id.*, 12. Hence, a POSA would have appreciated Xia's disclosure of multi-dose ophthalmic formulations containing a prostaglandin glaucoma agent that avoids the use of traditional preservatives, including BAC. Ex. 1002 ¶¶38, 46.

Schneider discloses an ophthalmic composition containing an effective amount of a prostaglandin ester therapeutic, travoprost, for the treatment of glaucoma. Ex. 1007, 9:21-42; Ex. 1002 ¶47. Travoprost itself, meets the limitations of both claims 5 and 6. Ex. 1002 ¶¶69-72. The composition is an aqueous solution at pH 6 ± 0.2 and contains several preservative components, including BAC (*id*.), a well-known traditional preservative that can be "toxic to the sensitive tissues of the eye." Ex. 1004, 1:49-55. A POSA would have appreciated that Schneider discloses an ophthalmic formulation containing the same active ingredient as the formulations of Xia, and therefore would have been motivated to combine Xia and Schneider in order to improve Schneider's ophthalmic formulation containing a glaucoma agent by removing BAC, a known source of toxicity, discomfort, and irritation to eye. Ex. 1002 ¶¶36, 47.

In making this change, a POSA would have sought to optimize the self-preservation and comfort of the formulation while maintaining the stability of the active agent, travoprost. *See, e.g.*, Ex. 1004, 1:64-66. A POSA replacing BAC

with zinc and optimizing the resulting formulation, would have retained as much of the travoprost formulation as feasible, as this was already an FDA-approved formulation, marketed as Travatan®. Ex. 1002 ¶¶46-47. As disclosed in Schneider, the travoprost (*i.e.*, Travatan®) formulation included other anti-microbial components besides BAC, including edetate disodium, tromethamine, and a borate-polyol system where the polyol is mannitol. Ex. 1007, 9:21-42. The concentration of boric acid (0.3 wt%) in the borate-polyol system falls within the claimed range. *Id.* To optimize the formulation, a POSA would not only have relied on his/her experience, but would have also looked to the disclosure of relevant references, such as Chowhan, which discloses ophthalmic preparations that contain borate and polyol at concentrations found in both Schneider and in claim 1 of the '299 patent. A POSA would have understood that the borate-polyol complexes have antimicrobial activity, are capable of increasing the activity of other antimicrobials (*see* Ex. 1004, 2:4-12), and were already being used for this purpose in the Schneider/Travatan® formulation. It would have been obvious to combine Chowhan with Xia and Schneider in order to optimize the borate-polyol portion of the self-preservation system and to arrive at the claimed invention for the reasons discussed below. Ex. 1002 ¶48.

Xia's zinc concentrations of "about 0.001 wt.%" and "about 0.005 wt.%" of a zinc compound such as zinc chloride fall within the claimed range. As explained

by Dr. Xia himself, these amounts of zinc chloride are equivalent to 0.074 mM and 0.37 mM of zinc ions. Ex. 1002 ¶50. In applying the zinc concentrations of Xia to the travoprost formulation of Schneider, a POSA would have had a reasonable expectation of success in view of the known effects of other agents for enhancing the anti-microbial efficacy of the formulation, and would have looked to take advantage of such agents. Among Schneider's agents is a borate-polyol complex which, as Chowhan explains, are known to "unexpectedly increase the antimicrobial efficacy of other antimicrobial agents when used in combination." *Id.*, 51; Ex. 1004, 2:10-12.

A POSA would have taken advantage of Schneider's borate-polyol complex to boost the anti-microbial efficacy of the zinc ions. Schneider discloses a boric acid concentration of 0.3 wt% and a mannitol concentration of 4.6 wt%, for a total of 4.9 wt%. Ex. 1007, 9:20-42. Schneider's concentrations fall within the range disclosed by Chowhan, which teaches a borate-polyol concentration of about 0.5 to about 6.0 percent by weight. Ex. 1004, 3:44-47. Chowhan's range also completely encompasses the total borate-polyol concentration range recited in claim 1. As a POSA would appreciate, claim 1 requires a range of 0.4% to 3.75% borate-polyol based on the total amounts of borate, propylene glycol, and sorbitol recited. Ex. 1002 ¶52. Furthermore, Chowhan teaches the ratios of borate to polyol disclosed in claim 1 of the '299 patent. Ex. 1002 ¶53. As before, based on

the total amounts of borate, propylene glycol, and sorbitol recited, claim 1 requires a borate-polyol ratio of 1:0.6 to 1:2.3, whereas Chowhan discloses a borate to polyol ratio of "preferably between about 1:0.25 and about 1:2.5." Ex. 1004, 3:34. Chowhan also states that "[s]uch optimum amount [of borate-polyol] can be readily determined by one skilled in the formulatory arts." Ex. 1004, 3:50-51. Therefore, the optimum amount of borate and polyol in the combination of Xia, Schneider, and Chowhan would have been readily determined by a POSA through routine experimentation.

Further, guided by Chowhan, a POSA would have had reason to optimize Schneider's borate-polyol complex to obtain a formulation containing propylene glycol and sorbitol at the concentrations claimed. Ex. 1002 ¶54. First, Schneider teaches the use of mannitol as part of a borate-polyol complex. Ex. 1007, 9:20-42. As is well known in the art, mannitol and sorbitol are sugars having identical chemical formulas and differing only in their stereochemistry at a single carbon and therefore share many similar physical properties. Ex. 1017, 5767, 8797. Second, Chowhan discloses that both mannitol and sorbitol, along with propylene glycol, are preferred polyols. Ex. 1004, 3:4-6. Third, Chowhan explains that mixtures of poylols may be used in borate-polyol complexes. Ex. 1004, 2:15-16, 3:10-13.

Starting from the concentrations in Schneider, a POSA would have had a

reason to optimize the borate, polyol, propylene glycol and sorbitol using the concentration ranges disclosed in Chowhan, as these components were result-effective variables known to affect the anti-microbial and other properties (*e.g.*, tonicity) of the composition. Ex. 1002 ¶54. As Chowhan states, optimum amounts of borate-polyol "can be readily determined by one skilled in the formulatory arts" (Ex. 1004, 3:50-51), and would have been within the skill of a POSA as these components were result-effective variables known to affect the properties of the solution. Ex. 1002 ¶54. A result-effective variable is a parameter which can be adjusted to achieve a result. *Application of Antonie*, 559 F.2d 618, 620 (CCPA 1977). The mere optimization of a result-effective variable is insufficient to render a claim patentable. *Peterson*, 315 F.3d at 1330. Moreover, "the prior art need not provide the exact method of optimization for the variable to be result-effective. A recognition in the prior art that a property is affected by the variable is sufficient to find the variable result-effective." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1297 (Fed. Cir. 2012).

Anionic species: As disclosed in Schneider, the only significant anionic species in Formulation A (the Travatan® formulation) is the borate-polyol complex. Ex. 1007, 9:21-42, claims 8, 11; Ex. 1002 ¶55. While Formulation A also contains edetate and any NaOH used to adjust the pH to 5.8 to 6.2, the amounts are negligible. At a pH of 6, the amount of NaOH would be about 0.01

uM—far below the 15 mM level of claim 1. *Id.* Further, in optimizing a self-preserved formulation containing zinc, a POSA would remove the edetate to avoid chelation of the zinc and interference with its antimicrobial properties. *Id.* Since the concentration of boric acid in Schneider's Formulation A is 0.3 wt%—within the claimed range—and the pH of the formulation is 5.8 to 6.2—within the '299 patent's preferred range of 5.0 to 6.0 (Ex. 1001, 9:56-60)—and the amounts and types of polyols disclosed in Chowhan also overlap the claimed range, one would expect the ionized fraction of borate-polyol complex of the optimized formulation would be less than 15 mM. *Id.*

Consistent with the absence of significant anionic species other than the borate-polyol complex of Schneider, the compositions disclosed in Xia and Chowhan do not require anionic species such as anionic buffers and chloride salts such as sodium chloride, but instead list such agents as being optional. For example, a POSA would have understood that both Xia and Chowhan disclose that their ophthalmic compositions are not necessarily isotonic, but that if tonicity is adjusted, it may be adjusted with agents other than sodium chloride (*e.g.*, glycerol). Ex. 1003, 10; Ex. 1004, 4:52. Thus, a POSA would have understood that the disclosures of Xia and Chowhan encompass formulations with chloride salt concentrations of zero or at least less than 15 mM. Ex. 1002 ¶56.

Similarly, the disclosure in Chowhan that phosphate anions can interfere

with antimicrobial activity (Ex. 1004, 1:45-48) would have guided a POSA to keep the concentration of anionic species as low as possible. Thus, Chowhan teaches that when anionic species are to be added to ophthalmic compositions, their concentrations should be kept as low as possible. Ex. 1002 ¶57.

During prosecution of the '299 patent, Alcon argued that Xia teaches away from the claims, alleging that Xia requires sodium chloride in its compositions and pointing the examiner to the examples of Xia, which include sodium chloride at a concentration of 37 mM. Ex. 1008, 364-365. But the passages from Xia cited above show that Xia does not require anionic species such as chloride salts in its disclosed compositions, and "disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure of non-preferred embodiments." *In re Susi*, 440 F.2d 442 (CCPA 1971).

Any attempt by Alcon to argue that Xia teaches away from the claims would be contradicted by the '299 patent itself, because it contains an admission that monovalent anions, such as the chloride in sodium chloride, have no effect on the antimicrobial activity of the composition, as evidenced by Examples AA and AB, which disclose identical base formulations except that example AB also contains 0.2 w/v% sodium chloride. Ex. 1001, 24:26-67. Thus, example AB includes 34.2 mM sodium chloride, whereas example AA lacks sodium chloride. Ex. 1002 ¶58. Despite differing in their concentration of monovalent

anions, the compositions of examples AA and AB have identical antimicrobial testing profiles. *Id.*; Ex. 1001, 25:1-29. So the data in the '299 patent show that an almost identical concentration of sodium chloride (34.2 mM) to that disclosed in the examples of Xia (37 mM) has no effect on antimicrobial activity. Ex. 1002 ¶59. Thus, the sodium chloride concentration disclosed in the examples of Xia does not teach away from the claims.

USP 27: A POSA would have recognized that a composition taught by the combination of Xia, Schneider and Chowhan would have inherently satisfied the USP 27 preservative efficiency requirements, and/or a POSA would have optimized the composition with the expectation of meeting such a standard. Ex. 1002 ¶¶60-62. As shown above, the combination of Xia, Schneider and Chowhan teaches a composition having the same components at the same concentrations as recited in claim 1. A POSA would have had a reasonable expectation that an ophthalmic composition having the same ingredients in the same amounts as claimed would have satisfied the USP 27 requirements from the teachings of Xia and Chowhan that compositions containing zinc and borate-polyol satisfied USP 27. *Id.*

Moreover, such an inherent property of a claimed composition does not impart patentability to claims and need not have been recognized by a POSA, as the Federal Circuit made clear in *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d

1344 (Fed. Cir. 2012). In *Santarus*, the patentee argued that claims to a method of treating a gastric acid disorder were not obvious because the claims recite achieving the desired results with low levels of sodium bicarbonate and achieving specific blood serum concentrations levels not disclosed in the prior art. *Id*., 1353. Nevertheless, the Court found the claims would have been obvious, noting that the prior art disclosed sodium bicarbonate ranges overlapping the claimed range. *Id*. at 1353-1354. The Court also found that the claimed blood serum concentrations did not overcome the finding of obviousness, stating that "[t]o hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Id*., 1354. The facts are identical here. The prior art teaches an ophthalmic composition having the same components at the concentrations claimed. The recitation that the claimed composition has sufficient antimicrobial activity to satisfy USP 27 requirements does not make the claims patentable.

Even if satisfying USP 27 requirements were not considered to be an inherent property of the compositions of the prior art, it would have only required a POSA's routine experimentation to prepare a composition that achieved USP 27 requirements as claimed. Ex. 1002 ¶62. A POSA would have understood that a multi-dose ophthalmic composition would have been required to pass an antimicrobial test at least as stringent as USP 27. *Id.* ¶61. A POSA

would have also had a reasonable expectation of success in formulating a composition that achieves USP 27's requirements. Schneider's travoprost formulation must meet USP 27 requirements as it was approved by the FDA as Travatan®. *Id.* ¶60. Xia teaches a formulation that satisfies USP 27 (Ex. 1003, 14), and Chowhan teaches a formulation that satisfies British Pharmacopoeia requirements (Ex. 1004, 9:32-64). A POSA would have had a reasonable expectation that a formulation based on a combination of these references would have similar antimicrobial properties, or that it could have been readily optimized to meet USP 27 requirements based on guidance in the references themselves. Ex. 1002 ¶60-62.

For at least the reasons above, Claims 1 and 4-6 would have been obvious to a POSA from the teachings of Xia, Schneider and Chowhan.

Claim 2: Claim 2 depends from claim 1 and further recites that the concentration of multivalent buffering anions is less than 5 mM. Claim 2 would have been obvious over Xia, Schneider and Chowhan. None of these references requires multivalent buffering anions. Ex. 1003, 12; Ex. 1004, 1:45-48; Ex. 1007, 9:21-42. A POSA would have had a reason to develop a composition with as low a concentration of multivalent buffering anions as possible because none are found in Schneider's travoprost formulation and Chowhan teaches that phosphate buffers can interfere with antimicrobial activity. Ex. 1002 ¶¶63-66.

Further, Alcon cannot show that the claimed range is critical compared to the teachings of the prior art, because the properties of the claimed composition would have been entirely expected from the teachings in the art. Ex. 1002 ¶¶58-59. There is no criticality in multivalent buffering anions at a concentration of less than 5 mM, and reciting this range does not make claim 2 patentable. *Peterson*, 315 F.3d at 1330.

Claims 7-8: Claim 7 depends from claim 1 and recites that the composition further comprises polyoxyl 40 hydrogenated castor oil wherein the composition has a pH from 5.5 to 5.9. Claim 8 depends from claim 1 and further recites that the composition comprises a non-ionic surfactant.

Claims 7 and 8 would have been obvious over Xia, Schneider and Chowhan. Ex. 1002 ¶¶73-79. Xia teaches "[s]urfactants, which are suitable for use in the present invention, are classified into … non-ionic surfactants" and teaches formulations having a preferred minimum pH of about 5 or about 6. Ex. 1003, 13. Schneider expressly teaches the use of polyethoxylated castor oils—which are nonionic surfactants—in prostaglandin compositions to enhance stability of the prostaglandin. Ex. 1007, 1:54-56. Further, Schneider expressly discloses the use of polyoxyl 40 hydrogenated castor oil in a travoprost ophthalmic formulation with a pH from 5.8 to 6.2. Ex. 1007, 2:11-34, 6:55-7:3, 9:21-42, claims 8, 11. A POSA therefore would have been motivated to retain polyoxyl 40 hydrogenated castor oil

in a zinc-containing travoprost formulation to stabilize the travoprost, and would have had a reasonable expectation of success in doing so because Xia teaches that nonionic surfactants may be used in zinc-containing ophthalmic formulations. Ex. 1002 ¶¶74, 79. Moreover, as the claimed pH range overlaps or is subsumed within the prior art range, claim 7 would have been *prima facie* obvious over the teachings of Xia, Schneider and Chowhan. Because the pH of an ophthalmic composition was known to affect the antimicrobial activity of the composition as of the EPPD of the '299 patent, a POSA would have had a reason to optimize this known pH variable to achieve the desired antimicrobial activity, as the prior art taught the claimed pH ranges and these ranges were known to affect antimicrobial activity. Ex. 1002 ¶75.

Alcon cannot show any criticality for the claimed pH range of 5.5 to 5.9 for two reasons. First, Alcon admits in the '299 patent that the wider pH range of 5.0 to 6.0—which overlaps both Xia's and Schneider's pH ranges—may be used to stabilize ophthalmic formulations containing polyethoxylated castor oil. Allegedly this range avoids particle formation by the castor oil impurity, 12-hydroxystearic acid (HSA). Ex. 1001, 9:56-60; Ex. 1002 ¶76.

Second, Alcon's own data in the '299 patent fails to support the criticality of any pH range. Table Y-2 of Example Y shows that the pH at which precipitate forms is dependent on the concentration of HSA impurity in the formulation. Ex.

1001, 22:50-23:34. The pH values 5.75 and 5.90 are squarely within the claimed range but still caused particle formation at 6.5 and 8 ppm HSA, whereas no particle precipitation was seen at pH 6.0 and 5 ppm HSA. *Id.* As particle formation appears primarily dependent on the concentration of HSA, the 5.5 to 5.9 pH range is not critical for the stability of the claimed formulation and would have been readily achieved by optimizing known compositions having pH values within this range. Ex. 1002 ¶77.

Claims 16 and 17: Claim 16 depends from claim 1 and recites that the concentration of anionic species is less than 10 mM. Claim 17 depends from claim 1 and recites that the concentration of anionic species is less than 5 mM. Claims 16 and 17 would have been obvious over Xia, Schneider and Chowhan. As discussed above for claim 1, none of Xia, Schneider or Chowhan requires anionic species other than borate, and Chowhan teaches that phosphate, an anionic species, can interfere with the activity of antimicrobials. *See also* Ex. 1002 ¶¶80-82. While Schneider discloses the use of edetate and NaOH in the travoprost formulation, as discussed above, a POSA would have removed the edetate to avoid zinc chelation and the concentration of hydroxide is negligible at pH 6 or below. *Id.* ¶55. Moreover, a POSA would have had a reason to develop a composition with as low a concentration of anionic species as possible – such as no anionic species – so as not to interfere with antimicrobial activity. A POSA

would have also known from the teachings of Xia that zinc has antimicrobial activity at the zinc concentrations claimed. Ex. 1003, 5. From the teachings that zinc has antimicrobial activity at low concentrations and that anionic species can interfere with this activity, a POSA would have had a reasonable expectation of success in arriving at the subject matter of claims 16 and 17. Ex. 1002 ¶¶80-85.

Claim 20: Claim 20 depends from claim 1 and recites that the composition comprises zinc ions at a concentration of 0.1 to 0.4 mM. Claim 20 would have been obvious over Xia and Chowhan. Ex. 1002 ¶¶86-87. As shown in the claim chart for claim 1 above, Xia teaches compositions containing zinc ions at a range of concentrations that overlaps the claimed range. As evidenced by Xia, the zinc ion concentrations recited in claim 20 were known in the art to have antimicrobial activity. Alcon cannot show that the claimed zinc concentrations are critical because antimicrobial activity at these concentrations in the claimed composition would have been entirely expected from the disclosures of Xia in view of Schneider and Chowhan. Ex. 1002 ¶61. *See Peterson*, 315 F.3d at 1330. Even if Alcon were to provide evidence of unexpectedly high antimicrobial activity for the claimed zinc concentrations, this would still not be enough to render the claims nonobvious given that a change in concentration from the prior art is not usually patentable unless "the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree

from the results of the prior art." *Aller*, 220 F.2d at 456.

For at least the above reasons, claims 1, 2, 4-8, 16, 17 and 20 would have been obvious over the combination of Xia, Schneider and Chowhan.

B. Ground 2: Claim 28 Would Have Been Obvious Over Xia, Schneider, the Travatan Label and Chowhan

Xia, Schneider and Chowhan are discussed above in Ground 1. FDA Approved Drug Label "TRAVATAN® (travoprost ophthalmic solution) 0.004% sterile" ("**TL**") (Ex. 1006) is copyrighted 2001. As evidenced by an Alcon SEC filing dated May 15, 2002, Travatan was launched in the U.S. in April 2001.[3] As a product must be sold with its label, the TL was publically available more than one year before the EPPD of the '299 patent. Ex. 1002 ¶41; *see also* 21 U.S.C. §352(b). Thus, the TL qualifies as prior art to the '299 patent under 35 U.S.C. §102(b). As illustrated in the claim chart and discussion below, claim 28 would have been obvious over Xia, Schneider, the TL and Chowhan.

A POSA would have combined Xia, Schneider and Chowhan for the reasons given above in Ground 1. A POSA would have also had a reason to combine the teaching of the TL with these references. Because the TL expressly lists Schneider at page 2, a POSA would understand that Schneider discloses and claims the Travatan® formulation and would look to the TL for the same reasons she would look to Schneider itself as discussed above in Ground 1.

[3] *See* Alcon, Inc.'s Form 6-K, filed May 15, 2002 at page 2 (Ex. 1016).

Claim 28: As shown by the following claim chart and discussion herein, claim 28 would have been obvious over Xia, Schneider, the TL and Chowhan. From the teachings of these references, a POSA would have arrived at the composition of claim 28 using only routine experimentation. Further, the concentration ranges disclosed in Xia, the TL and Chowhan overlap the claimed concentrations, establishing a prima facie case of obviousness.

'299 patent	**Disclosure of Xia, Schneider, the TL and Chowhan**
28. A multi-dose, self-preserved ophthalmic composition, consisting of:	See chart for claim 1 above.
travoprost at a concentration of 0.004% w/v;	"Ophthalmic therapeutic agents include all ophthalmic agents, which can be topically applied. Such ophthalmic therapeutic agents include … **prostaglandins**." Ex. 1003, 12. "Each mL of TRAVATAN® 0.004% contains 40 ug travoprost," and "Travoprost is a synthetic prostaglandin." Ex. 1006, 1. Formulation A is an opthlamic solution containing **travoprost**. Ex. 1007, 9:20-42.
zinc chloride ionized in the composition at a concentration of 0.0025% w/v;	"[T]he composition has a minimum of **about 0.001 wt.%**, **about 0.005 wt.%**, … of a zinc compound per total weight of the composition"…"Preferably, the zinc compound is selected from the group comprising zinc citrate and zinc chloride." Ex. 1003, 5.

polyoxyl 40 hydrogenated castor oil at a concentration of 0.5% w/v;	"Surfactants, which are suitable for use in the present invention, are classified into … **nonionic surfactants**…." Ex. 1003, 13. "Inactive ingredients are: **polyoxyl 40 hydrogenated castor oil**…." Ex. 1006, 1.
borate and polyol,	See chart for claim 1 above.
the borate being present in the composition as boric acid at a concentration of 1.0% w/v and	Examples 2 and 3 in Xia contain **0.850 wt.% boric acid**. Ex. 1003, 17-18. "[B]orate-polyol complexes are formed by mixing **boric acid** … with polyols." Ex. 1004, 2:15-16. "[B]orate-polyol complexes … in an amount between about **0.5 to about 6.0 percent** by weight (wt %), preferably between about **1.0 to about 2.5 wt %**." Ex. 1004, 3:43-46.
the polyol including propylene glycol and sorbitol,	See chart for claim 1 above.
the propylene glycol being present in the composition at a concentration of 0.75% w/v and	See chart for claim 1 above.
the sorbitol being present in the composition at a concentration of 0.25% w/v;	See chart for claim 1 above.
sodium hydroxide and/or hydrochloric acid to adjust pH; and	Example 1 of Chowhan discloses use of sodium hydroxide and hydrochloric acid to adjust pH. Ex. 1004, 4:17-32.
water;	"[T]he total amount of **water in the composition** is a minimum of about 95 wt.%...." Ex. 1003, 13.

wherein; (i) the composition has a concentration of anionic species less than 15 mM; and	See chart for claim 1 above.
(ii) the composition exhibits sufficient antimicrobial activity to allow the composition to satisfy USP 27 preservative efficacy requirements.	See chart for claim 1 above.

As discussed in Ground 1 and shown in the claim charts above, the combination of Xia, Schneider, and Chowhan teaches antimicrobial ophthalmic compositions having the claimed components at the claimed concentrations. As shown in the claim chart above, the TL also teaches travoprost at the claimed concentration of 0.004 %w/v and (along with Schneider) teaches the non-ionic surfactant polyoxyl 40 hydrogenated castor oil. Ex. 1006, 1. Thus, the combination of Xia, Schneider, Chowhan and the TL teaches an ophthalmic composition having all of the components claimed. Ex. 1002 ¶90.

Alcon has demonstrated no unexpected properties related to the specific concentrations claimed, and a POSA would be able to arrive at the optimal concentrations of these known result-effective components through only routine experimentation. Ex. 1002 ¶¶88-95.

For example, Alcon has not demonstrated that it is unexpected that zinc has

antimicrobial activity at low concentrations. Nor can it, because it was well known as of the EPPD of the '299 patent that zinc has antimicrobial activity at low concentrations. Also, Alcon has not demonstrated any unexpected result provided by the specific concentration of 0.5% w/v polyoxyl hydrogenated castor oil, which is expressly disclosed in Schneider's travoprost formulation. Ex. 1002 ¶¶89-90; Ex. 1007, 9:21-42.

Anionic species: As discussed for claim 1 in Ground 1, none of Xia, Schneider, or Chowhan requires anionic species at the concentration claimed. The TL also does not disclose significant concentrations of anionic species. A POSA would have known from the teachings of Chowhan that certain anionic species can reduce the activity of antimicrobial agents. Ex. 1002 ¶93. From the teachings of Chowhan, a POSA would have had a reason to develop ophthalmic compositions free of multivalent buffering anions. *Id.*

USP 27: For the same reasons discussed in Ground 1, a POSA would have recognized that a composition taught by the combination of Xia, Schneider, and Chowhan would have inherently satisfied USP 27. Ex. 1002 ¶61. A POSA would have also had a reasonable expectation that the combination of Xia, Schneider and Chowhan would produce an ophthalmic composition satisfying the USP 27 requirements. Ex. 1002 ¶¶61, 82.

The combination of Xia, Schneider, Chowhan and the TL teach

antimicrobial ophthalmic compositions having the components recited in claim 28. Thus, as confirmed by Dr. Xia, a POSA would have had a reasonable expectation of success in formulating an antimicrobial ophthalmic composition as recited in claim 28 from the teachings of Xia, Schneider, the TL, and Chowhan. Ex. 1002 ¶95.

C. Ground 3: Claims 1-23 and 25-26 Would Have Been Obvious Over Xia, Schneider, Chowhan and Gadd

Xia, Schneider and Chowhan are discussed above in Grounds 1 and 2. Gadd *et al.*, "Microorganisms and Heavy Metal Toxicity," *Microbial Ecology*, 4:303-317 (1978) (Ex. 1005), published in 1978, long before the EPPD of the '299 patent. Thus, Gadd qualifies as prior art to the '299 patent under 35 U.S.C. §102(b). Gadd teaches that anions, such as chelating compounds and multivalent buffering anions, as well as multivalent metal cations can interfere with the antimicrobial activity of zinc, and thus it provides further reason to avoid such anions and multivalent metal cations other than zinc in the composition. Ex. 1005, 307; Ex. 1002 ¶¶40, 97-99, 137, 140.

A POSA would have had reason to combine Gadd with Xia, Schneider and Chowhan. As discussed above in Ground 1, a POSA would have combined the teachings of Xia, Schneider and Chowhan to avoid the use of BAC in an ophthalmic composition containing the glaucoma agent, travoprost. Because Xia teaches zinc as an antimicrobial agent, and Gadd discloses the antimicrobial

activity of zinc in growth media and the effects of ions on zinc's antimicrobial activity, a POSA would have looked to Gadd for guidance on maximizing the antimicrobial activity of zinc. Because Gadd teaches that ions can interfere with the activity of antimicrobial agents, a concern also expressed by Chowhan, a POSA would have been motivated to minimize or avoid ions that reduce the antimicrobial effectiveness of zinc. Ex. 1005, 306-307; Ex. 1004, 1:45-48; Ex. 1002 ¶¶82, 98-99, 142. Because the cited references teach or suggest each of the claimed limitations, and because a POSA would have had a reason to combine the teachings of the cited references and arrive at the claimed invention through routine optimization, claims 1-23 and 25-26 would have been obvious over Xia, Schneider, Chowhan and Gadd.

Claims 1, 22 and 26: Claims 1, 22, and 26 would have been obvious over Xia, Schneider, Chowhan and Gadd. Ex. 1002 ¶¶97-99, 137-142. As shown in the claim chart and detailed in Ground 1, Xia, Schneider, and Chowhan disclose all of the components of the ophthalmic composition of claim 1 at the concentrations claimed. Similarly, these references teach the additional limitations of claims 22 and 26, including an effective amount of travoprost (Ex. 1003, 12; Ex. 1007, 9:21-42), 0.1-0.4 mM zinc ions provided by zinc chloride (Ex. 1003, 5), boric acid at 0.5 to 1.2% w/v (Ex. 1003, 16; 1004, 2:55-57, 3:44-47), and water (Ex. 1003, 13). Ex. 1002 ¶¶137-141. Xia

and Schneider also teach or suggest the claim 26 limitations of a pH of 5.5-5.9 and polyoxyl 40 hydrogenated castor oil for the same reasons discussed above for claim 7 in Ground 1. *See also* Ex. 1002 ¶¶139, 141. Further, as discussed below, Gadd would have motivated a POSA to keep the concentrations of anionic species, multivalent anions, and multivalent cations other than zinc below the claimed limits of claims 1, 22 and 26.

Anionic species: For the reasons discussed in Ground 1, from the teachings of Xia, Schneider and Chowhan, a POSA would have had reason to keep the concentration of anionic species low. Further, Gadd expressly discloses that anionic species, including those "which can chelate metals" and those which form precipitates such as phosphate, thiosulfate, carbonate and bicarbonate, reduce metal toxicity to microorganisms. Ex. 1005, 307. As confirmed by Dr. Xia, a POSA would have known from the teachings of Chowhan and Gadd that certain anionic species, such as multivalent buffering anions, can reduce the activity of antimicrobial agents. Accordingly, from the teachings of Gadd, as well as Chowhan, a POSA would have had a reason to develop ophthalmic compositions with low concentrations of anions. Ex. 1002 ¶¶97-99, 137, 140.

Multivalent buffering anions and multivalent metal cations: Regarding claims 22 and 26, Gadd teaches that multivalent buffering anions,

such as phosphate, thiosulfate, carbonate and bicarbonate, can interfere with the activity of antimicrobial agents, including metals such as zinc. Ex. 1004, 1:45-48; Ex. 1005, 307. Gadd also teaches that multivalent metal cations, such as magnesium, can interfere with the antimicrobial activity of zinc. Ex. 1005, 306. None of Xia, Schneider, Chowhan and Gadd require metal ions other than zinc. The concept of ions interfering with antimicrobial agents was well known in the art, and the teachings of Chowhan and Gadd would have provided a reason to a POSA to avoid multivalent buffering anions and multivalent metal cations in ophthalmic compositions containing zinc as an antimicrobial agent. Ex. 1002 ¶¶ 137, 140.

USP 27: For the reasons discussed above in Ground 1, a POSA would also have recognized that a composition taught by the combination of Xia, Schneider, Chowhan and Gadd would have inherently satisfied the USP 27 preservative efficiency requirements, or would have optimized such a composition to do so. Ex. 1002 ¶142.

To the extent a POSA would have needed to optimize concentrations of any of the components in the claimed compositions, only routine optimization would have been needed for the reasons discussed in Ground 1. Each component of the claimed compositions was used for its known function as discussed herein and shown in the accompanying claim charts, and was

therefore known to be a result-effective variable.

For at least the reasons above and as shown in the chart below, Claims 1, 22, and 26 would have been obvious to a POSA from the teachings of Xia, Schneider, Chowhan and Gadd.

'299 patent	**'299 patent**	**'299 patent**	**Prior Art Disclosure**
1. A multi-dose, self-preserved ophthalmic composition, comprising:	**22.** A multi-dose, self- preserved ophthalmic composition comprising:	**26.** A multi-dose, self-preserved ophthalmic composition, consisting of:	See chart for claim 1, Ground 1.
	an effective amount of travoprost;	an effective amount of travoprost;	"composition is an ophthalmic solution that optionally includes…**therapeutic agents**"… [including] "**glaucoma agents**… [and] **prostaglandins**…." Ex. 1003, 3, 12. Schneider's ophthalmic formulation A contains **0.001-0.005% w/v travoprost**. Ex. 1007, 9:20-42; Ex. 1002 ¶¶37, 70, 94.

'299 patent	**'299 patent**	**'299 patent**	**Prior Art Disclosure**
zinc ions at a concentration of 0.04 to 0.4 mM; and	zinc ions at a concentration of 0.1 to 0.4 mM wherein the zinc ions are provided by zinc chloride;	zinc ions at a concentration of 0.1 to 0.4 mM wherein the zinc ions are provided by zinc chloride;	See chart for claim 1, Ground 1.
		polyoxyl 40 hydrogenated castor oil;	See chart for claim 28, Ground 2.
borate and polyol,	borate and polyol,	borate and polyol,	See chart for claim 1, Ground 1.
the borate being present in the composition at a concentration of 0.1 to 2.0% w/v and	the borate being present as boric acid in the composition at a concentration of 0.5 to 1.2% w/v and	the borate being present as boric acid in the composition at a concentration of 0.5 to 1.2% w/v and	See chart for claim 1, Ground 1.
the polyol being present in the composition at a concentration of 0.25 to 2.5% w/v,			See chart for claim 1 in Ground 1.
	the polyol including propylene glycol and sorbitol	the polyol including propylene glycol and sorbitol	"comfort agents such as … **propylene glycol** can also be added." Ex. 1003, 14. "Preferred polyols are … **propylene glycol and sorbitol**." Ex. 1004, 3:4-6.

'299 patent	**'299 patent**	**'299 patent**	**Prior Art Disclosure**
the polyol comprising propylene glycol in the composition at a concentration of 0.25 to 1.25% w/v and	the propylene glycol being present in the composition at a concentration of 0.25 to 1.25% w/v and	the propylene glycol being present in the composition at a concentration of 0.25 to 1.25% w/v and	See chart for claim 1 in Ground 1.
sorbitol in the composition at a concentration of 0.05 to 0.5% w/v; wherein	the sorbitol being present in the composition at a concentration of 0.05 to 0.5% w/v; and	the sorbitol being present in the composition at a concentration of 0.05 to 0.5% w/v; and	See chart for claim 1 in Ground 1.
	water	water	Formulation A of Schneider contains purified water "q.s. to 100%." Ex. 1007, 9:21-42. "[T]he total amount of **water in the composition** is a minimum of about 95 wt.%..." Ex. 1003, 13.

’299 patent	’299 patent	’299 patent	Prior Art Disclosure
(i) the composition has a concentration of anionic species less than 15 mM; and	wherein: (i) the composition has a concentration of anionic species less than 10 mM;	wherein: (i) the composition has a concentration of anionic species less than 10 mM;	See chart for claim 1 in Ground 1. “Anions are able **to reduce metal toxicity** [to microoganisms] by precipitation…. Phosphate, thiosulfate, carbonate and bicarbonate ions can form precipitates with heavy metals depending on their concentrations….” Ex. 1005, 307.
(ii) the composition exhibits sufficient antimicrobial activity to allow the composition to satisfy USP 27 preservative efficacy requirements.	(ii) the composition exhibits sufficient antimicrobial activity to allow the composition to satisfy USP 27 preservative efficacy requirements; and	(ii) the composition exhibits sufficient antimicrobial activity to allow the composition to satisfy USP 27 preservative efficacy requirements;	See chart for claim 1 in Ground 1.

'299 patent	**'299 patent**	**'299 patent**	**Prior Art Disclosure**
	(iii) the composition does not contain multivalent buffering anions and does not contain multivalent cations other than zinc.	(iii) the composition does not contain multivalent buffering anions and does not contain multivalent cations other than zinc; and	"Anions are able **to reduce metal toxicity** [to microorganisms] by precipitation…. **Phosphate, thiosulfate, carbonate and bicarbonate ions** [multivalent buffering anions] can form precipitates with heavy metals depending on their concentrations…." Ex. 1005, 307. "Cations such as **magnesium and calcium** [multivalent metal cations] can often **reduce heavy metal inhibition**. Toxic effects of … zinc . . . to *Escherichia coli* were decreased in media with a high **magnesium** content." Ex. 1005, 306.

'299 patent	**'299 patent**	**'299 patent**	**Prior Art Disclosure**
		(iv) the composition has a pH from 5.5 to 5.9.	Xia teaches an ophthalmic formulation having a minimum **pH of about 5** and a maximum **pH of about 7.8**. Ex. 1003, 12. Schneider discloses ophthalmic formulation having a pH of 5.8 to 6.2. Ex. 1007, 9:21-42, claims 8, 11.

Claim 2: Claim 2 depends from claim 1 and further recites that the concentration of multivalent buffering anions is less than 5 mM. A POSA would have found claim 2 obvious over the combination of Xia, Schneider, Chowhan and Gadd.

As discussed above for claim 1, neither Xia nor Chowhan requires the presence of multivalent buffering anions, but each discloses such agents as optional; Schneider omits them altogether from its travoprost formulation. Ex. 1003, 10; Ex. 1004, 4:52; Ex. 1007, 9:21-42. Chowhan teaches that multivalent buffering anions can interfere with the activity of antimicrobials. Gadd provides a POSA with further reason to maintain a low concentration of anionic species, as Gadd teaches that multivalent buffering anions can interfere with the antimicrobial

activity of zinc. Ex. 1005, 307. A POSA would therefore have had a reason to develop ophthalmic compositions with low concentrations of multivalent buffering anions from the teachings of these references. Ex. 1002 ¶¶100-101.

Claim 3: Claim 3 depends from claim 1 and further recites that the composition has a concentration of multivalent buffering anions that is less than 5 mM and a concentration of multivalent metal cations other than zinc that is less than 5 mM. Claim 3 would have been obvious to a POSA over the teachings of Xia, Chowhan and Gadd. For the reasons discussed above for claim 2, an ophthalmic composition with a concentration of multivalent buffering anions that is less than 5 mM would have been obvious over Xia, Chowhan and Gadd.

A POSA reading Gadd would have also had a reason to maintain a concentration of multivalent metal cations other than zinc of less than 5 mM, as Gadd teaches that "[c]ations such as magnesium and calcium [multivalent metal cations] can often reduce heavy metal inhibition [of microorganisms]. Toxic effects of … zinc … to *Escherichia coli* were decreased in media with a high magnesium content." Ex. 1005, 306. From the teachings of Gadd, a POSA would have tried to keep the concentration of multivalent metal cations other than zinc as low as possible. Ex. 1002 ¶¶102-104.

Claims 4-6: Claims 4-6 depend directly or indirectly from claim 1 as discussed above in Ground 1 and recite an effective amount of a therapeutic agent

(claim 4) such as travoprost (claims 5, 6), among others. For the reasons given above, claim 1 would have been obvious over Xia, Schneider, and Chowhan. Since Schneider and Xia teach all of the limitations of claims 4-6 for the reasons given in Ground 1, claims 4-6 would also have been obvious over Xia, Schneider, Chowhan and Gadd. Ex. 1002 ¶¶105-107.

Claims 7, 8: As discussed above in Ground 1, Xia and Schneider teach or suggest all of the limitations of Claims 7 and 8. Since claims 7 and 8 each depend from claim 1, they would have been obvious over the combination of Xia, Schneider, Chowhan and Gadd for similar reasons to those given in this Ground for claim 1. Ex. 1002 ¶¶108-111.

Claim 9: Claim 9 depends from claim 1 and recites that the composition further comprises an effective amount of a therapeutic agent, a concentration of multivalent buffering anions that is less than 5 mM, a concentration of multivalent metal cations other than zinc that is less than 5 mM, and borate at a concentration of 0.5 to 1.2% w/v. Claim 9 would have been obvious over Xia, Schneider, Chowhan and Gadd for the following reasons. Both Schneider and Xia teach ophthalmic compositions comprising effective amounts of therapeutic agents. Ex. 1003, 12; Ex. 1007, 1:13-20, 2:8-14. Concentrations of less than 5 mM multivalent buffering anions and less than 5 mM multivalent metal cations would have been obvious from the teaching of Xia, Schneider Chowhan and Gadd for the

reasons discussed for claims 2 and 3 above. As discussed above for claims 22 and 26 in this Ground, Xia and Chowhan disclose borate concentrations within or overlapping the claimed range. Ex. 1002 ¶¶112-118.

Claims 10, 11: Claim 10 depends from claim 9 and, like claim 4, recites that the composition further comprises a therapeutic agent selected from the group consisting of bimatoprost, latanoprost, travoprost and unoprostone. Similarly claim 11 depends from claim 9 and, like claim 6, specifies that the therapeutic agent is travoprost. As shown above in this ground, claim 9 would have been obvious over Xia, Schneider, Chowhan and Gadd. Likewise, as shown in Ground 1 for claims 5 and 6, Schneider teaches an ophthalmic formulation with 0.001 and 0.005% (w/v) travoprost, an effective amount. Ex. 1002 ¶¶119-121. A POSA would have combined Xia and Schneider because Xia indicates that its zinc self-preservation technology can be applied to ophthalmic formulations containing glaucoma agents, *e.g.*, prostaglandins, and travoprost is both a prostaglandin and a glaucoma agent. *Id.*

Claim 12: Claim 12 depends from claim 11 and, like claim 7, recites that the composition further comprises polyoxyl 40 hydrogenated castor oil wherein the composition has a pH from 5.5 to 5.9. For the same reasons discussed for claim 7 in Ground 1 and claim 26 above, a composition comprising polyoxyl 40 hydrogenated castor oil having a pH of 5.5 to 5.9 would have been obvious over

the teachings of Xia, Schneider, Chowhan and Gadd. *Id.* ¶¶122-123.

Claim 13: Claim 13 depends from claim 9 and recites that the zinc ions are provided by zinc chloride at a concentration of 0.001 to 0.005 w/v%. Claim 13 would have been obvious over Xia, Schneider, Chowhan and Gadd. Xia teaches compositions containing zinc salts at concentrations of a "minimum of about 0.001 wt.%, about 0.005 wt.%, about 0.01 wt.% or about 0.05 wt.% of a zinc compound per total weight of the composition" and Xia teaches zinc chloride. Ex. 1003, 5. The range of zinc concentrations taught by Xia overlaps those recited in claim 13, rendering the claims *prima facie* obvious. A POSA would have arrived at the claimed composition by routinely optimizing the concentration of zinc chloride—a known result-effective variable—disclosed by Xia. Ex. 1002 ¶¶124-125. As evidenced by Xia, zinc was known to act as an antimicrobial at the claimed concentration range, and the claimed concentration range provides no unexpected result. Ex. 1003, 4-5. Zinc chloride was a well-known antimicrobial agent and was a known result effective variable as of the EPPD of the '299 patent and optimizing the concentration of zinc would have been within the skill of a POSA. Ex. 1002 ¶125.

Claim 14: Claim 14 depends from claim 9 and recites that the propylene glycol is present in the composition at a concentration of 0.75 w/v%, the borate is boric acid and is present in the composition at a concentration of 1.0

w/v% and the zinc ions are provided by zinc chloride at a concentration of 0.0025 w/v%. Claim 14 would have been obvious over Xia, Schneider, Chowhan and Gadd.

Given the concentrations recited in claim 14, the total claimed borate-polyol concentration ranges from 1.8 to 2.25 % (1.0% borate + 0.75 % propylene glycol + 0.05 or 0.5 % sorbitol). Chowhan teaches adding polyols, such as propylene glycol, as part of a borate-polyol complex, and a preferred total borate-polyol concentration range from 1.0 wt% to 2.5 wt%. Ex. 1004, 3:44-51. Thus, the total borate-polyol concentration range of claim 14 is completely subsumed by the total borate-polyol concentration range disclosed in Chowhan. For the same reasons shown for claim 1 in Ground 1, the ratios of borate to polyol recited in claim 14 were already taught by Chowhan. Ex. 1002 ¶¶126-128.

The zinc concentration recited in claim 14 (0.0025% provided by zinc chloride) falls within the range disclosed by Xia. Xia teaches compositions containing zinc salts at concentrations of a "minimum of about 0.001 wt.%, about 0.005 wt.%, … of a zinc compound per total weight of the composition," and teaches zinc chloride. Ex. 1003, 5. As discussed for claim 13 above, a POSA would have had a reasonable expectation of success in arriving at the claimed invention by optimizing the concentration of zinc chloride, a known result-effective variable. Ex. 1002 ¶129. Thus, claim 14 would have been obvious from the disclosures of Xia, Schneider, Chowhan, and Gadd.

Claim 15: Claim 15 depends from claims 1 and 9 and recites that the composition does not contain multivalent buffering anions and does not contain multivalent metal ions other than zinc. Claim 15 would have been obvious over Xia, Schneider, Chowhan and Gadd. As discussed above for claims 2 and 3, Chowhan and Gadd teach that multivalent buffering anions, such as phosphate, can interfere with the activity of antimicrobial agents, including metals such as zinc. Ex. 1004, 1:45-48; Ex. 1005, 307. Gadd further teaches that multivalent metal cations, such as magnesium, can interfere with the antimicrobial activity of zinc. Ex. 1005, 306. Chowhan and Gadd would have motivated a POSA to form a zinc-containing ophthalmic composition free of multivalent buffering anions and multivalent metal cations, as it was known that such ions could interfere with the antimicrobial activity of zinc. Ex. 1002 ¶¶130-131.

Claims 16-19: Claim 16 depends from claim 1, and claim 18 depends from claim 9. Claims 16 and 18 recite that the concentration of anionic species is less than 10 mM. Claim 17 depends from claim 1, and claim 19 depends from claim 9; Claims 17 and 19 recite that the concentration of anionic species is less than 5 mM. Claims 16-19 would have been obvious over the combination of Xia, Schneider, Chowhan and Gadd.

As discussed above for claims 1, 22, and 26, Chowhan teaches that

anionic species can interfere with the activity of antimicrobials and Gadd teaches that anionic species can interfere with the antimicrobial activity of zinc. Ex. 1004, 1:45-48; Ex. 1005, 307. As anionic species were known to interfere with the antimicrobial activity of zinc, a POSA would have had a reason to develop a composition with as low a concentration of anionic species as possible. Ex. 1002 ¶¶98-99, 133-134. A POSA would have also known from the teachings of Xia that zinc has antimicrobial activity at the zinc concentrations claimed. Ex. 1003, 4-5. From the teachings that zinc has antimicrobial activity at low concentrations and that anionic species can interfere with this activity, a POSA would have had a reasonable expectation of success in arriving at the subject matter of claims 16-19. Ex. 1002 ¶¶132-134.

Claims 20 and 21: Claim 20 depends from claim 1 and claim 21 depends from claim 9. Both claims recite that the composition comprises zinc ions at a concentration of 0.1 to 0.4 mM. As shown in the claim charts for claim 1, Xia, Schneider, Chowhan, and Gadd would have rendered claim 1 obvious. Likewise as shown above in this section, claim 9 would have been obvious over Xia, Schneider, Chowhan, and Gadd. Claims 20 and 21 would have been obvious over the combination of Xia, Schneider, Chowhan and Gadd for the following reasons.

Xia teaches compositions containing zinc ions at a range of concentrations

that overlaps the zinc concentrations recited in claims 20 and 21. As evidenced by Xia, the zinc ion concentrations recited in dependent claims 20 and 21 were known in the art to have antimicrobial activity. Alcon cannot show that unexpected results are achieved at the claimed zinc concentrations because antimicrobial activity at these concentrations would have been entirely expected from Xia. Ex. 1002 ¶¶135-136. Further, as discussed for claim 20 in Ground 1 above, even if Alcon were to provide evidence of unexpectedly high antimicrobial activity for the claimed zinc concentrations, this showing would still not be enough to render the claims nonobvious as an unexpected result must be different in kind and not merely in degree from the prior art in order to render a claim nonobvious.

Claim 23: Claim 23 depends from claim 22 and, like claim 7 and 26, further recites that the composition comprises polyoxyl 40 hydrogenated castor oil and that the composition has a pH from 5.5 to 5.9. As discussed for claim 7 in Ground 1 and claim 26 above, a composition comprising polyoxyl 40 hydrogenated castor oil having a pH of 5.5 to 5.9 would have been obvious over the teachings of Xia and Schneider. For the same reasons, claim 23 would have been obvious over the combination of Xia, Schneider, Chowhan and Gadd in view of the teachings in Xia and Schneider concerning polyoxyl 40 hydrogenated castor oil and pH. Ex. 1002 ¶¶143-144.

Claim 25: Claim 25 depends from claim 22 and recites that the composition does not contain multivalent buffering anions and does not contain multivalent cations other than zinc. As claim 22 already contains this limitation, the claim is likely indefinite for failure to further limit the subject matter of the claim from which it depends. However, as indefiniteness is not a ground upon which IPR can be instituted, Petitioner asserts that claim 25 would have been obvious over Xia, Schneider, Chowhan and Gadd for the same reasons claim 22 would have been obvious with respect to these limitations and for the same reasons claim 15 would have been obvious. *Id.* ¶¶145-146.

For at least the above reasons, claims 1-23 and 25-26 would have been obvious over the combination of Xia, Schneider, Chowhan and Gadd.

D. Ground 4: Claims 24 and 27-28 Would Have Been Obvious Over Xia, Schneider, the TL, Chowhan and Gadd

Xia, Schneider and Chowhan are discussed in Ground 1. The TL is discussed in Ground 2. Gadd is discussed in Ground 3. As illustrated in the claim charts and discussed below, claims 24 and 27-28 would have been obvious over Xia, the TL, Chowhan and Gadd.

As discussed above in Ground 1, a POSA would have had a reason to combine the teachings of Xia, Schneider, and Chowhan. A POSA would have combined them with the teachings of the TL and Gadd because Xia teaches an ophthalmic composition containing a prostaglandin as the active agent, and the TL

discloses an ophthalmic composition containing the prostaglandin travoprost as the active agent. Ex. 1003, 12; Ex. 1006, 1. The TL also teaches an ophthalmic composition containing borate-polyol as an antimicrobial agent as set forth in Chowhan. Ex. 1004, 3:44-47; Ex. 1006, 1. As discussed in Ground 3, Gadd discusses early research on zinc as an antimicrobial agent, and Xia teaches zinc as an antimicrobial agent. Ex. 1005, 306-307; Ex. 1003, 4-5. Thus, a POSA would have looked to the TL for a known prostaglandin to use in the compositions of Xia and would have looked to Chowhan for information on the borate-polyol systems disclosed on the TL. A POSA would have also looked to the teaching of Gadd to determine how the antimicrobial activity of zinc taught by Xia might be modified. Ex. 1002 ¶98-99. This reason to combine applies to all claims in this Ground.

Claim 24: Claim 24 depends from claim 23 and recites that the concentration of travoprost in the composition is 0.004% w/v, the concentration of zinc chloride ionized in the composition is 0.0025% w/v, the concentration of boric acid is 1.0% w/v, the concentration of propylene glycol in the composition is 0.75% w/v, the concentration of sorbitol in the composition is 0.25 w/v%, and the concentration of non-ionic surfactant in the composition is 0.5 w/v%. These concentrations are the same as those recited in claim 28, and claim 24 similarly would have been obvious over Xia, Schneider, the TL, Chowhan and Gadd for the

reasons discussed below.

Claim 23 would have been obvious over Xia, Schneider, Chowhan and Gadd for the reasons discussed above in Ground 3. The components recited in claim 24 are taught by Xia, Schneider, the TL and Chowhan as shown in the claim chart for claim 28 in Ground 2. As discussed for claim 28 in Ground 2, Alcon has demonstrated no unexpected properties related to the specific concentrations claimed, and a POSA would be able to determine the optimal concentrations of these components through only routine experimentation. Further, a POSA would have had a reasonable expectation of success in arriving at the optimal concentrations of these components as their functions in ophthalmic compositions were already known. Ex. 1002 ¶¶90-95, 147-150. Thus, claim 24 would have been obvious over the combination of Xia, Schneider, the TL, Chowhan and Gadd.

Claims 27 and 28:

'299 patent	**'299 patent**	**Disclosure of Xia, Schneider, the TL, Chowhan and Gadd**
27. A multi-dose, self-preserved ophthalmic composition, consisting of:	**28.** A multi-dose, self-preserved ophthalmic composition, consisting of:	See chart for claim 28 in Ground 2.
travoprost at a concentration of 0.004% w/v;	travoprost at a concentration of 0.004% w/v;	See chart for claim 28 in Ground 2.

ionized zinc chloride at a concentration of 0.0025% w/v	zinc chloride ionized in the composition at a concentration of 0.0025% w/v	See chart for claim 28 in Ground 2.
polyoxyl 40 hydrogenated castor oil at a concentration of 0.5% w/v;	polyoxyl 40 hydrogenated castor oil at a concentration of 0.5% w/v;	See chart for claim 28 in Ground 2.
borate and polyol,	borate and polyol,	See chart for claim 28 in Ground 2.
the borate being present as boric acid in the composition at a concentration of 1.0% w/v and	the borate being present in the composition as boric acid at a concentration of 1.0% w/v and	See chart for claim 28 in Ground 2.
the polyol including propylene glycol and sorbitol,	the polyol including propylene glycol and sorbitol,	See chart for claim 28 in Ground 2.
the propylene glycol being present in the composition at a concentration of 0.75% w/v and	the propylene glycol being present in the composition at a concentration of 0.75% w/v and	See chart for claim 28 in Ground 2.
the sorbitol being present in the composition at a concentration of 0.25% w/v;	the sorbitol being present in the composition at a concentration of 0.25% w/v;	See chart for claim 28 in Ground 2.
sodium hydroxide and/or hydrochloric acid to adjust pH; and	sodium hydroxide and/or hydrochloric acid to adjust pH; and	See chart for claim 28 in Ground 2.
water;	water;	See chart for claim 28 in Ground 2.

wherein; (i) the composition has a concentration of anionic species less than 5 mM;	wherein; (i) the composition has a concentration of anionic species less than 15 mM; and	See chart for claim 1 above. "Anions are able **to reduce metal toxicity** [to microoganisms] by precipitation…. phosphate, thiosulfate, carbonate and bicarbonate ions can form precipitates with heavy metals …" Ex. 1005, 307.
(ii) the composition exhibits sufficient antimicrobial activity to allow the composition to satisfy USP 27 preservative efficacy requirements;	(ii) the composition exhibits sufficient antimicrobial activity to allow the composition to satisfy USP 27 preservative efficacy requirements.	See chart for claim 1 above.
(iii) the composition does not contain multivalent buffering anions and does not contain multivalent cations other than zinc; and		See discussion for claim 2 in Ground 1 and claims 1-3 in Ground 3. The ingredients of Formulation A of Schneider (Ex. 1007, 9:21-42) and on the Travatan Label (Ex. 1006, 1) do not include multivalent buffering anions or multivalent cations.
(iv) the composition has a pH from 5.5 to 5.9.		"The **pH** of the composition of one embodiment of the present invention is a minimum of about **5**, about **6.0**..." Ex. 1003, 12. Schneider discloses ophthalmic formulation having a pH of 5.8 to 6.2. Ex. 1007,

Claims 27-28: As shown in the claim charts above, the combination of Xia,

the TL, Chowhan and Gadd teaches all of the components of claims 22 and 26-28, and these claims would have been obvious over this combination of references. As discussed at the beginning of this Ground, a POSA would have had a reason to combine all four references. As discussed for claim 1 in Ground 1, the combination of Xia and Chowhan teaches antimicrobial ophthalmic compositions having the claimed components at the claimed concentrations. As discussed for claims 1-3 in Ground 2, a POSA would have known from the teachings of Chowhan and Gadd that anionic species, such as phosphate, can reduce the activity of antimicrobial agents. Ex. 1004, 1:45-48; Ex. 1005, 307.

A POSA would have had a reasonable expectation of success in arriving at the claimed subject matter from the disclosures of Xia, the TL, Chowhan and Gadd. As shown in the claim charts above, Xia, the TL and Chowhan disclose all of the components of the ophthalmic composition claimed. Xia teaches that compositions with low concentrations of zinc satisfy USP 27 preservative requirements, while Chowhan teaches borate-polyol systems that satisfy British Pharmacopeia requirements. Ex. 1003, 3, 14-15, 17-18; Ex. 1004, 9:38-41. Xia and Chowhan also teach that zinc and borate-polyol can enhance the activity of other antimicrobials. Ex. 1003, 5; Ex. 1004, 2:10-12. A POSA would have had a reasonable expectation of success based on the combination of Xia, Chowhan and the TL in producing a composition with antimicrobial activity. And that

expectation of success would have been enhanced by Gadd's teachings that ions can interfere with antimicrobial activity and should be kept to a minimum concentration. Ex. 1002 ¶¶151, 152, 154.

Anionic species: As discussed in Grounds 1-3, neither Xia, Chowhan, the TL nor Gadd require multivalent buffering anions in their disclosed compositions. A POSA would have known from the teachings of Chowhan and Gadd that certain anionic species can reduce the activity of antimicrobial agents. Ex. 1004, 1:45-48; Ex. 1005, 306-307; Ex. 1002 ¶¶151, 152, 154. Thus, from the teachings of Chowhan and Gadd, a POSA would have had a reason to develop ophthalmic compositions free of anionic species. Ex. 1002 ¶¶151-154.

Multivalent buffering anions and multivalent metal cations: Regarding claims 22, 26 and 27, as discussed above for claims 1-3 in Ground 2, Chowhan and Gadd teach that multivalent buffering anions, such as phosphate, can interfere with the activity of antimicrobial agents, including metals such as zinc. Ex. 1004, 1:45-48; Ex. 1005, 307. Gadd further teaches that multivalent metal cations, such as magnesium, can interfere with the antimicrobial activity of zinc. Ex. 1005, 306. As shown in the claim chart above, none of Xia, the TL, Chowhan and Gadd require metal ions other than zinc. The concept of ions interfering with antimicrobial agents was well known in the art, and the teachings of Chowhan and Gadd would have provided a reason to a POSA to not include either multivalent

buffering anions or multivalent metal cations in ophthalmic compositions containing zinc as an antimicrobial agent. Ex. 1002 ¶¶151-155.

pH: Regarding the pH limitation of claims 26 and 27, as discussed for claim 7 in Ground 3, the TL teaches an ophthalmic composition having a pH of approximately 6.0. Ex. 1006, 1. Xia teaches an ophthalmic composition having a preferable minimum pH of 5.0 or 6.0. Ex. 1003, 12. As of the EPPD of the '299 patent, the pH of an ophthalmic composition was known to affect the antimicrobial activity of the composition, and POSA would have had a reason to optimize the pH of a composition with a reasonable expectation of success. Ex. 1002 ¶156. For at least the reasons above, as confirmed by Dr. Xia, claims 27 and 28 would have been obvious. Ex. 1002 ¶¶151-160.

IX. NO SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS

If Alcon does present secondary evidence of nonobviousness in its preliminary response, the Board should refuse consideration of that evidence, and institute trial, because "detailed consideration of [a patentee's] secondary consideration evidence may not be undertaken until [the petitioner] has had an opportunity to test it." *Amneal Pharms. v. Supernus Pharms.*, IPR2013-00368, at 12-13 (PTAB Dec. 17, 2013) (granting IPR despite submission of district court evidence of secondary considerations in preliminary response). Nevertheless, the Federal Circuit has repeatedly held that even relevant secondary considerations

supported by substantial evidence often fail to overcome a strong *prima facie* case of obviousness, which is the case here. *See, e.g.*, *Leapfrog Enterprises Inc. v. Fisher-Price Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

A. No Unexpected Results Compared To Closest Prior Art

During prosecution of the ’299 patent, Alcon argued that ophthalmic compositions comprising a combination of propylene glycol at a concentration of 0.25 to 1.25% w/v, sorbitol at a concentration of 0.05 to 0.5% w/v with a low concentration of zinc ions, and anionic species achieved preservative efficiency “without any substantial assistance from any other antimicrobial agents.” Ex. 1008, 367. But, as shown throughout this petition, none of these results were surprisingly superior over the closest prior art, which is the Xia reference. A showing that the claimed compositions satisfy USP 27 does not demonstrate unexpected superiority as compared to Xia’s compositions because Xia’s compositions satisfy an antimicrobial test that is even more stringent than the USP 27 requirements. Ex. 1003, 5, 15. Alcon’s results are not surprisingly superior – especially in view of Xia’s teaching that zinc is capable of enhancing the antimicrobial activity of other agents, and Chowhan’s identical teaching concerning borate-polyol complexes. Ex. 1002 ¶163.

B. No Long-Felt Unmet Need

In an earlier-settled IPR of the ’299 patent, Alcon submitted a declaration by

Dr. Richard Parrish (Ex. 1022) to argue that TRAVATAN Z® satisfied a long-felt need for a "BAK-free antiglaucoma drug that would not lead to an increased risk of the exacerbation of OSD [ocular surface disease] symptoms with chronic use." This argument lacks factual and legal merit.

First, this alleged need is not commensurate with the scope of the claims of the '299 patent, none of which are limited to treatment of glaucoma whatsoever, whether for chronic or non-chronic treatment, or for patients suffering from a BAC-allergy or OSD. Ex. 1021 ¶15. Thus, Alcon cannot establish nexus based on a long-felt need for the chronic treatment of glaucoma, given that the claims are not limited to any treatment whatsoever. *See Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014) ("[E]vidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support.").

Second, Dr. Parrish did not provide any evidence of unsuccessful efforts to solve the problem associated with formulating a BAC-free ophthalmic composition. *See* MPEP 716.04 (citing *Orthopedic Equipment Co., Inc. v. All Orthopedic Appliances, Inc.*, 707 F.2d 1376 (Fed. Cir. 1983) (Although the claimed invention achieved the desirable result of reducing inventories, there was no evidence of any prior unsuccessful attempts to do so.) Even if such evidence did exist, the Xia reference expressly teaches self-preserved, antimicrobial ophthalmic compositions that are free of BAC.

Third, any alleged long-felt need for a BAC-free antiglaucoma medication was much more modest than Dr. Parrish describes in his declaration. Unlike Dr. Parrish, Dr. Yvonne Buys prescribes TRAVATAN Z® as a first-line treatment only to a niche population of patients who were known to be allergic to BAC, rather than to patients suffering from OSD. Ex. 1021 ¶12; Ex. 1026, 391. Only around 8% of patients suffer from a BAC allergy, which is about half the percentage of individuals age 65 and over that Dr. Parrish says suffer from OSD and to whom he prescribes TRAVATAN Z® as a first-line treatment. Ex. 1021 ¶12. Indeed, Dr. Parrish does not explain why he prescribes TRAVATAN Z® to this broader group, given that OSD may be caused by the active ingredient of the drug itself, rather than by the preservative BAC. *Id.*

Fourth, Dr. Parrish does not adequately support his assertion that TRAVATAN Z® satisfied the long-felt need. Dr. Parrish fails to mention that approximately 10% of patients do not respond to TRAVATAN® Z and that an even larger percentage show an insufficient response to the drug. *Id.* ¶13; Ex. 1025, 351; Ex. 1024, 704. Thus, Dr. Parrish's declaration is deficient insofar as he has not explained what percentage of patients taking TRAVATAN Z® achieve an adequate response without undesirable side effects.

Fifth, Dr. Parrish cites no long-term study on the chronic use of TRAVATAN Z® to support his assertion that TRAVATAN Z® does not result in

an increased risk of the exacerbation of OSD symptoms with chronic use. Ex. 1021 ¶14.

C. No Commercial Success

In the earlier-settled IPR, Alcon submitted a declaration by Dr. Henry Grabowski (Ex. 1037) to argue that TRAVATAN Z® is commercially successful. Dr. Grabowski's analysis is flawed, however, given that there was no evidence provided on the pricing of TRAVATAN Z® relative to the price of its competitors. Dr. Grabowski fails to mention that the price of TRAVATAN Z® was greatly impacted by Alcon's rebate program, which was offered as early as June 2008 and still continues today. Ex. 1027-1028 ($25 off TRAVATAN Z® prescription in June 2008 and April 2009, respectively); Ex. 1029 ($20 off the next four prescriptions in March 2010); Ex. 1030 (pay no more than $25 for each 30-day supply of TRAVATAN Z® through December 2011); Ex. 1031 (pay no more than $25 for each 30-day supply of TRAVATAN Z® through March 2013); Ex. 1032 (save up to $1,300 on medication refills and to pay as little as $25 for each 30-day supply of prescribed eyedrops through December 2013); Ex. 1033-1036 (discounts through an OPENINGS Patient Support Program savings card from 2014-2017). Through this extensive rebate program, patients have received and continue to receive significant discounts off the retail price of TRAVATAN Z®, which reduced the price advantage that generics would normally enjoy over the branded

drug. *See Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1101 (Fed. Cir. 2015) (affirming district court's finding of no nexus where commercial success was due in part to patentee's "introducing a series of rebates to stimulate sales of the drug").

In addition, Dr. Grabowski improperly restricts the relevant market to "the glaucoma market and ophthalmic prostaglandin analogs." Ex. 1037. Alcon cannot limit its objective evidence to only prostaglandin analogs in the treatment of glaucoma when the claims are not limited to glaucoma. *See Allergan*, 754 F.3d at 965 (requiring objective evidence to be commensurate in scope with the claims).

Furthermore, Dr. Grabowski also fails to provide any evidence "as to what sales would normally be expected in the market." *Ex parte Jellá,* 90 USPQ2d 1009, 1012 (BPAI 2008) (precedential). Without any record evidence of what level of sales should have been expected to which the actual sales of TRAVATAN Z® can be compared, Alcon has not borne the burden of production on commercial success. *Torrent Pharms. V. Novartis AG*, IPR2014-00784, Paper 12, at 30 (PTAB Sept. 24, 2015). Regardless, even a highly successful product cannot alone overcome the strong showing of obviousness that Argentum has made in this case. *Media Techs. Licensing, LLC v. Upper Deck Co.*, 596 F.3d 1334, 1339 (Fed. Cir. 2010).

X. CONCLUSION

For the foregoing reasons, each of claims 1-28 would have been obvious over the art discussed above, notwithstanding any assertions of secondary considerations. Petitioner respectfully requests that trial be instituted and that the challenged claims be canceled.

Respectfully submitted,

Dated: March 10, 2017

By: /Michael R. Houston/

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that this brief complies with the type-volume limitations of 37 CFR § 42.24(a)(1)(i). This brief (excluding mandatory notices, table of contents, table of authorities, certificate of service or word count, and appendix of exhibits) contains 13,944 words as calculated by the "Word Count" feature of Microsoft Word 2010, the word processing program used to create it, and manual counting of the annotations in any figures.

The undersigned further certifies that this brief complies with the typeface requirements of 37 CFR § 42.6(a)(2)(ii) and typestyle requirements of 37 CFR § 42.6(a)(2)(iii). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14-point font.

Respectfully submitted,

Dated: March 10, 2017

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CERTIFICATION OF SERVICE

The undersigned hereby certifies that the above-captioned "Petition for *Inter Partes* Review of U.S. Patent No. 8,268,299 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123," including its supporting evidence (Exs. 1001-1037), was served in its entirety on March 10, 2017, upon the following parties via USPS Express Mail:

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
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Dated: March 10, 2017

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