

Filed on behalf of OmniActive Health Technologies, Inc.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

OMNIACTIVE HEALTH TECHNOLOGIES, INC.,
Petitioner,

v.

KEMIN INDUSTRIES, INC.,
Patent Owner

Case No. to Be Assigned
Patent No. 8,815,955

**PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,815,955
UNDER 35 U.S.C. §§311–319 AND 37 C.F.R. §42.100 *et seq.***

TABLE OF CONTENTS

I.	Introduction.....	1
II.	Mandatory Notices (37 C.F.R. §42.8(a)(1)).....	5
	A. Real Party-in-interest (37 C.F.R. §42.8(b)(1)).....	5
	B. Notice of Related Matters (37 C.F.R. §42.8(b)(2)).....	5
	C. Lead and Back-up Counsel (37 C.F.R. §42.8(b)(3)).....	6
	D. Service Information (37 C.F.R. §42.8(b)(3)).....	6
III.	Fees (37 C.F.R. §42.103).....	6
IV.	Requirements for IPR Under 37 C.F.R. §42.104.....	7
	A. Grounds for Standing (37 C.F.R. §42.104(a)).....	7
	B. Prior Art Publications Relied Upon.....	7
	C. Claims and Statutory Grounds (37 C.F.R. §§42.104(b)(1) &(b)(2)).....	8
V.	Summary of the '955 Patent.....	9
	A. Overview.....	9
	B. Prosecution History.....	14
VI.	Level of Ordinary Skill in the Art.....	14
VII.	Claim Construction.....	14
VIII.	Summary of References Applied in This Petition.....	16
	A. Snider (Ex. 1003).....	17
	B. McLaughlan (Ex. 1004).....	20
	C. Chaine (Ex. 1005).....	22
	D. Richer (Ex. 1006).....	23

E.	Ciolkowski (Ex. 1007)	25
IX.	The Challenged Claims Are Unpatentable	25
A.	Summary of Obviousness Arguments.....	26
B.	Ground I - Claims 1–6 and 9 of the '955 Patent are unpatentable as obvious over Snider.....	29
1.	Claim 1 (preamble) - “A method of treating the increased age-related macular degeneration present in a subject having age-related macular degeneration and either hyperopia or astigmatism, relative to the age-related macular degeneration present in a subject having age-related macular degeneration but neither hyperopia nor astigmatism, comprising”	29
2.	Claim 1 (body) - “administering to the subject having the macular degeneration and either the hyperopia or astigmatism a composition comprising a therapeutically effective amount of one or more ocular antioxidants.”	35
3.	Claim 2 - “The method of claim 1, wherein said ocular antioxidant is selected from the group consisting of antioxidant vitamins, carotenoids, antioxidant minerals, natural antioxidant extracts and synthetic antioxidants.”	37
4.	Claim 4 - “The method of claim 2, wherein the carotenoid is selected from the list consisting of lutein, zeaxanthin, beta-carotene, retinoids, retinal, retinaldehyde, and meso-zeaxanthin.”	39
5.	Claim 9 - “The method of claim 2, wherein said therapeutically effective amount of said carotenoid is between 0.0001 and 2 mg per kilogram of body weight of said subject per day.”	40
6.	Claim 3 - “The method of claim 2, wherein said antioxidant vitamin is selected from the list consisting of vitamins A, C, and E.”	41

7.	Claim 5 - “The method of claim 2, wherein said antioxidant mineral is selected from the list consisting of zinc, copper, and selenium.”	43
8.	Claim 6 - “The method of claim 2, wherein said natural extract is selected from the list consisting of polyphenols, quercitin, anthocyanins, and anthocyanidins.”	44
C.	Ground II - Claims 8, 10, and 12 of the ’955 Patent are unpatentable as obvious over the combination of Snider and Richer.	45
1.	Claim 8 - “The method of claim 2, wherein said therapeutically effective amount of said antioxidant vitamin is between 0.02 (1 IU) and 15 mg (150 IU) per kilogram of body weight of said subject per day.”	45
2.	Claim 10 - “The method of claim 2, wherein said therapeutically effective amount of said antioxidant mineral is between 0.0001 and 5 mg per kilogram of body weight of said subject per day.”	48
3.	Claim 12 - “The method of claim 2, wherein said therapeutically effective amount of said natural extract is between 0.0001 and 20 mg per kilogram of body weight of said subject per day.”	51
D.	Ground III - Claims 7, 11, and 13 of the ’955 Patent are unpatentable as obvious over the combination of Snider and Ciolkowski.....	54
1.	Claim 7 - “The method of claim 2, wherein said synthetic antioxidant is selected from the list consisting of BHT, BHA, and BTHQ.”	54
2.	Claim 11 - “The method of claim 2, wherein said therapeutically effective amount of said synthetic antioxidant is between 0.001 and 15 mg per kilogram of body weight of said subject per day.”	57
3.	Claim 13 - “The method of claim 2, wherein said therapeutically effective amount of said synthetic	

antioxidant is between 0.0001 and 20 mg per kilogram of
body weight of said subject per day.” 60

X. Conclusion 63

LIST OF EXHIBITS

Exhibit	Description
Ex. 1001	U.S. Patent No. 8,815,955 (“the ’955 Patent”)
Ex. 1002	Prosecution History of the ’955 Patent
Ex. 1003	Lloyd Snider, Evidence Supports New Approaches for Reducing the Risk of Macular Degeneration, <i>Optometric Management</i> (November 2008) (“Snider”)
Ex. 1004	Barbara McLaughlan, Awareness of Age-related Macular Degeneration and Associated Risk Factors, AMD Alliance International (September 2005) (“McLaughlan”)
Ex. 1005	Gilles Chaine, Case-control study of the risk factors for age related macular degeneration, <i>British Journal of Ophthalmology</i> (September 1998) (“Chaine”)
Ex. 1006	Stuart Richer, Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial), <i>Optometry</i> (April 2004) (“Richer”)
Ex. 1007	U.S. Patent Application Publication No. US 2009/0239836 to Ciolkowski (“Ciolkowski”)
Ex. 1008	Declaration of Dr. John Landrum
Ex. 1009	<i>Curriculum Vitae</i> of Dr. John Landrum
Ex. 1010	Declaration of Rachel Watters A
Ex. 1011	Declaration of Rachel Watters B
Ex. 1012	Declaration of Raymond Weschler
Ex. 1013	WIPO International Publication No. WO2007118095 A2
Ex. 1014	Shirley Sarkes, Relationship of Basal Lamina Deposit and Membranous Debris to the Clinical Presentation of Early Age-Related Macular Degeneration, <i>Investigative Ophthalmology & Visual Science</i> (March 2007)
Ex. 1015	John T. Landrum & Richard A. Bone, Chapter 22: Mechanistic Evidence for Eye Diseases and Carotenoids, <i>Carotenoids in Health and Disease (Oxidative Stress and Disease)</i> (September 30, 2004)
Ex. 1016	Johanna M. Seddon, MD, et al., Dietary Carotenoids, Vitamins A, C, and E, and Advanced Age-Related Macular Degeneration, <i>The JAMA Network</i> (November 9, 1994)

Petition for Inter Partes Review of U.S. Patent No. 8,815,955

Exhibit	Description
Ex. 1017	K. Kirschfeld, Carotenoid pigments: their possible role in protecting against photooxidation in eyes and photoreceptor cells, <i>Proc. R. Soc. Lond.</i> (1982)
Ex. 1018	Werner K. Noell, et al., Retinal damage by light in rats, <i>Invest. Ophthalmol. Visual Sci</i> (October 1966)
Ex. 1019	William T. Ham, Jr., et al., Histologic analysis of photochemical lesions produced in rhesus retina by short-wave-length light., <i>Invest. Ophthalmol. Visual Sci</i> (October 1978)
Ex. 1020	W. T. Ham, Jr., Basic mechanisms underlying the production of photochemical lesions in the mammalian retina, <i>Current Eye Research</i> (1984)
Ex. 1021	John J. Weiter, M.D., et al., Central Sparing in Annual Macular Degeneration, <i>American Journal of Ophthalmology</i> (September 1988)
Ex. 1022	Anna Pawlak, et al., Action spectra for the photoconsumption of oxygen by human ocular lipofuscin and lipofuscin extracts, <i>Archives of Biochemistry and Biophysics</i> (2002)
Ex. 1023	[reserved]
Ex. 1024	Michael A. Sandberg, PhD, Hyperopia and Neovascularization in Age-related Macular Degeneration, <i>Ophthalmology</i> (July 1993)
Ex. 1025	M. Kamran Ikram, et al., Relationship between Refraction and Prevalent as well as Incident Age-Related Maculopathy: The Rotterdam Study, <i>Invest. Ophthalmol. Visual Sci.</i> (September 2003)
Ex. 1026	Richard A. Bone, et al., Macular Pigment in Donor Eyes with and without AMD: A Case-Control Study; <i>Invest. Ophthalmol. Visual Sci.</i> (January 2001)
Ex. 1027	John T. Landrum, et al., A One Year Study of the Macular Pigment: The Effect of 140 Days of Lutein Supplement, <i>Exp. Eye Res.</i> (1997)
Ex. 1028	Yin Chen, A Study of Carotenoids Uptake in Human Subjects and Their Metabolites, <i>Thesis - Florida International University</i> (1999)
Ex. 1029	Richard A. Bone & John T. Landrum, Dose-dependent response of serum lutein and macular pigment optical density to supplementation with lutein esters, <i>Elsevier</i> (June 2010)
Ex. 1030	John T. Landrum & Richard A. Bone, Carotenoid nutrition and the human retina, <i>Int'l J. of Integrative Med.</i> (May/June 2000)

Petition for Inter Partes Review of U.S. Patent No. 8,815,955

Exhibit	Description
Ex. 1031	Richard A. Bone, et al., Lutein and Zeaxanthin Dietary Supplements Raise Macular Pigment Density and Serum Concentrations of these Carotenoids in Humans, <i>J. Nutr.</i> (2003)

I. Introduction

OmniActive Health Technologies, Inc. (“Petitioner”) petitions for *Inter Partes* Review (“IPR”) seeking cancellation of claims 1–13 (“challenged claims”) of U.S. Patent No. 8,815,955 (Ex. 1001, “the ’955 Patent”), assigned to Kemin Industries, Inc.

The ’955 Patent “relates generally to a method of early diagnosis and treatment of ocular disorders and, more specifically, to the early diagnosis of subjects at risk for age-related macular degeneration [(“AMD”)] and the administration of ocular antioxidants to subjects having hyperopia, presbyopia or astigmatism.” Ex. 1001, 1:10–15. AMD “is a disease that affects the central vision necessary for reading, facial recognition, and other fine visually associated tasks.” Ex. 1008, ¶14. AMD worsens gradually as a result of “oxidative damage in the central retina,” which is protected against such damage by the macular pigment. *Id.* at ¶¶34, 28. The macular pigment is “composed principally of three carotenoids: Lutein; R,R-Zeaxanthin; and R,S-Zeaxanthin [meso-zeaxanthin].” *Id.* at ¶18.

The ’955 Patent acknowledges the long-understood use of ocular antioxidants to treat AMD based on the “definite relationship between the ingestion of ocular antioxidants and a reduction in the risk for the incidence and/or progression of AMD.” Ex. 1001, 5:7–9. The ’955 Patent does not purport to

disclose any new forms of treatment; rather, it purports to “address the link between hyperopia, presbyopia, and/or astigmatism and AMD.” *Id.* at 11:25–27. Hyperopia, presbyopia, and astigmatism are eye conditions. Hyperopia is also known as “farsightedness.” *Id.* at 2:56. Presbyopia is an “age-related visual disorder that affects virtually everyone to some extent” that results in “improper focus of the image upon the retina.” *Id.* at 2:64–3:5. Astigmatism is a defect of the cornea or the lens in which there is “irregular curvature to one or both of these structures.” *Id.* at 3:30–33.

The claims of the ’955 Patent are directed to a method of treating AMD present in a subject “comprising administering to the subject . . . a composition comprising a therapeutically effective amount of one or more ocular antioxidants.” In the face of the long-established practice of using antioxidants to treat AMD, the Examiner allowed the claims of the ’955 Patent only after they were amended to address treatment of the so-called “*increased* age-related macular degeneration present in a *subject having age-related macular degeneration and either hyperopia or astigmatism, relative to the age-related macular degeneration in a subject having age-related macular degeneration but neither hyperopia nor astigmatism.*” Ex. 1002, 14–15 (emphasis added).

Notably, rather than disclose any original science regarding the matter, the inventor of the ’955 Patent acknowledged that this purported link between AMD

and presbyopia, hyperopia, and astigmatism “is based upon the *known effects* of the cornea and lens of the eye in relation to the focusing light of upon the retina [and] the *available information* on ocular disorders including AMD.” Ex. 1001, 4:16–21 (emphasis added).

As admitted by the inventor, both “the factors associated with [the] incidence [of AMD]” and “the reported effect of ocular antioxidants in helping to reduce the progression of AMD” were well known at the time. *Id.* at 4:21–26. The inventor acknowledged that a person of ordinary skill in the art (“POSA”) would have understood that blue light and oxidative damage contributed to the development of AMD, noting that “[a]lthough this theory of macular damage associated with the blue wavelengths of visible light has long been speculated, proof that these wavelengths actually damage retinal tissue has only recently been demonstrated in-vivo.” *Id.* at 5:26–30. The inventor further recognized that “[the prior-art Richer and AREDS studies] along with a plethora of other results from in-vitro, ex-vivo, and animal and human studies[,] support a definite relationship between the ingestion of ocular antioxidants and a reduction in the risk for the incidence and/or progression of AMD.” *Id.* at 5:5–9. These prior-art studies also demonstrate that vitamins, minerals, and carotenoids were among the ocular antioxidants that would be effective for such treatment. *See id.* at 4:33–5:9. Moreover, the ’955 Patent concedes that information regarding the purported

“relationship between hyperopia, presbyopia and astigmatism, Age-Related Macular Degeneration (AMD) and ocular antioxidants” was available through other references and known in the field at the time. *See id.* at 4:16–28.

So what is the purported inventive contribution of the '955 Patent? As noted above, and as conceded by the inventor, it is not any new method of treatment, not any new composition, and not any new scientific principle purportedly discovered by the inventor through original science. Rather, the problem purportedly addressed by the '955 Patent is that “no publications or references have been identified relating all of these factors in a unified manner.” Ex. 1001, 4:28–30. The prior art cited in this petition demonstrates that statement to be wrong. Prior publications such as the Snider article (Ex. 1003) did combine these teachings “in a unified manner.”

Based on the knowledge and teachings available at the time, and as reflected in Snider, a POSA would have understood that: (1) hyperopia was a risk factor associated with the development of AMD, (2) eye-care practitioners “determine[] the need for interventional supplementation therapy [with ocular antioxidants] based on . . . risk factors for [A]MD the patient may have,” including hyperopia, and (3) treatment with ocular antioxidants “correlated with a decreased rate of progression” of AMD, such that there is a “very compelling case for placing every patient at any stage of [A]MD on a triple carotenoid supplement.” *See* Ex. 1003, 3,

6. A POSA therefore would have had motivation to administer ocular antioxidants to subjects with hyperopia and AMD (i.e., subjects with purported “increased age-related macular degeneration”) as claimed by the ’955 Patent. Moreover, based on the successful treatment of AMD patients using ocular antioxidants in previous studies, a POSA would have reasonably expected such administration to be successful in treating AMD in subjects with hyperopia and AMD, as claimed. *See* Ex. 1008, ¶53. Therefore, as shown in detail below, the prior art shows the claims of the ’955 Patent were obvious at the time of the alleged invention.

II. Mandatory Notices (37 C.F.R. §42.8(a)(1))

A. Real Party-in-interest (37 C.F.R. §42.8(b)(1))

The real parties in interest for this IPR petition are Petitioner OmniActive Health Technologies, Inc. and OmniActive Health Technologies Ltd.

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

The ’955 Patent is the subject of a complaint under 19 U.S.C. §1337 against Petitioner in the International Trade Commission (ITC), captioned *Certain Food Supplements and Vitamins, Including Ocular Antioxidants and Components Thereof and Products Containing the Same*, Inv. No. 337-TA-3177. In addition, the ’955 Patent is the subject of a civil action in the District of New Jersey for declaratory judgment of non-infringement filed by Petitioner against Patent Owner in *OmniActive Health Technologies, Inc. v. Kemin Industries, Inc.*, Civil Action No. 16-4988.

C. Lead and Back-up Counsel (37 C.F.R. §42.8(b)(3))

Lead Counsel is David A. Garr (Reg. No. 74,932); T: (202) 662-5250; F: (202) 778-5250; E: dgarr@cov.com. Backup Counsel is Jay I. Alexander (Reg. No. 32,678); T: (202) 662-5622; F: (202) 778-5622; jalexander@cov.com. The postal and hand delivery address for the foregoing counsel is: Covington & Burling LLP, One CityCenter, 850 Tenth Street, NW, Washington, DC 20001.

D. Service Information (37 C.F.R. §42.8(b)(3))

Service information is provided in the designation of counsel above. Counsel for Petitioner consents to service of all documents via electronic mail at OmniActive-Kemin@cov.com.

III. Fees (37 C.F.R. §42.103)

The undersigned authorizes the United States Patent and Trademark Office (“Office”) to charge \$23,000 (\$9,000 request fee, and \$14,000 post-institution fee) to Deposit Account No. 50-0740 for the fees set forth in 37 C.F.R. §42.15(a) for this Petition for *Inter Partes* Review. The undersigned also authorizes payment for any additional fees that might be due in connection with this Petition to be charged to the Deposit Account.

IV. Requirements for IPR Under 37 C.F.R. §42.104

A. Grounds for Standing (37 C.F.R. §42.104(a))

Pursuant to 37 C.F.R. §42.104(a), Petitioner certifies that the '955 Patent is available for IPR and that Petitioner is not barred or estopped from requesting an IPR challenging the '955 Patent on the grounds identified in the present petition.

B. Prior Art Publications Relied Upon

Exhibit	Reference	Publication Date	Availability as Prior Art
1003	Lloyd Snider, Evidence Supports New Approaches for Reducing the Risk of Macular Degeneration, <i>Optometric Management</i> (“Snider”)	November 2008	35 U.S.C. §102(b)
1004	Barbara McLaughlan, Awareness of Age-related Macular Degeneration and Associated Risk Factors, AMD Alliance International Global Report 2005 (“McLaughlan”)	September 2005	35 U.S.C. §102(b)
1005	Gilles Chaine, Case-control study of the risk factors for age	September 1998	35 U.S.C. §102(b)

	related macular degeneration, <i>British Journal of Ophthalmology</i> (“Chaine”)		
1006	Stuart Richer, Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial), <i>Optometry</i> (“Richer”)	April 2004	35 U.S.C. §102(b)
1007	U.S. Patent Application Publication No. 2009/0239836 (“Ciolkowski”)	September 24, 2009	35 U.S.C. §102(a) & (e)

C. Claims and Statutory Grounds (37 C.F.R. §§42.104(b)(1) &(b)(2))

Ground	Claims	Basis
I	'955 Patent claims 1–6, and 9	Under 35 U.S.C. §103 as

		unpatentable over Snider
II	'955 Patent claims 8, 10, and 12	Under 35 U.S.C. §103 as unpatentable over Snider and Richer
III	'955 Patent claims 7, 11, and 13	Under 35 U.S.C. §103 as unpatentable over Snider and Ciolkowski

V. Summary of the '955 Patent

A. Overview

The '955 Patent (Ex. 1001), entitled “Methods of Treating Ocular Disorders,” issued on August 26, 2014 from U.S. Patent Application No. 13/238,939 (“the '939 Application”), which was filed on September 21, 2011. The '939 Application claims priority through a parent application to U.S. Provisional Application No. 61/384,958, filed on September 21, 2010.¹ Therefore, any documents published before September 21, 2009 are prior art under 35 U.S.C.

¹ Petitioner reserves the right to challenge the priority date in subsequent legal proceedings.

§102(b).² Documents published before September 21, 2010 are prior art under 35 U.S.C. §102(a). Issued United States patents and United States patent application publications filed before September 21, 2010 are prior art under 35 U.S.C. §102(e).

The '955 Patent contains 13 claims, all of which are challenged in this petition. The '955 Patent relies on prior studies in the field of ocular nutrition demonstrating “a definite relationship between the ingestion of ocular antioxidants and a reduction in the risk for the incidence and/or progression of AMD.” Ex. 1001, 5:7–9. More specifically, the '955 Patent cites multiple studies demonstrating the successful treatment of AMD “as a result of lutein and zeaxanthin supplementation or a combination of these xanthophylls with other antioxidants.” *Id.* at 4:37–39.

Acknowledging the known practice of treating AMD with ocular antioxidants (specifically the macular pigments lutein and zeaxanthin), the '955 Patent clarifies that “[t]he methods of the present invention are not meant to cover damage that might be induced in the eye as a result of other conditions/diseases

² Because the '939 Application was filed prior to March 16, 2013, the provisions of 35 U.S.C. §102 prior to the amendments of the America Invents Act (“AIA”) apply. Therefore, all references to 35 U.S.C. §102 herein are to the pre-AIA version.

[other than hyperopia, presbyopia, or astigmatism] that might also result in AMD, including but not limited to inherited conditions (a genetic component) or damage from other forms of retinopathies aside from AMD.” Ex. 1001, 11:20–25.

The ’955 Patent characterizes the “present invention” as “the administration to subjects having or at risk for having hyperopia, presbyopia or astigmatism with a composition having a therapeutically effective amount of ocular antioxidants, including specifically macular pigments, to prevent, treat, or delay the onset of AMD.” Ex. 1001, 1:32–37. In addition, the ’955 Patent states that an “increased risk of developing AMD consist[s] of the existence or risk for the existence of hyperopia, presbyopia or astigmatism.” *Id.* at 1:38–40. The alleged inventive concept involves presentation, in a “unified manner,” of (i) the relationship between AMD and hyperopia, presbyopia, and astigmatism³ and (ii) the effects of

³ The ’955 Patent states that “[t]he epidemiological literature contains conflicting reports of a relationship between hyperopia and AMD with one report indicating that people who exhibit hyperopia are more likely to get AMD in later life and other reports indicated [sic] that such a relationship was weak at best.” Ex. 1001, 7:4-7 (internal citations omitted). Despite some conflicting studies in the field regarding a causal link between hyperopia and AMD, prior art to the ’955 Patent (continued...)

“ocular antioxidants in helping reduce the progression of AMD.” Ex. 1001, 4:16–32.

Claims 1–13 at issue in this petition are directed to methods of treating “the increased age-related macular degeneration present in a subject having age-related macular degeneration and either hyperopia or astigmatism” by administering ocular oxidants, including the carotenoids lutein and zeaxanthin. Claim 1, the lone independent claim of the ’955 Patent, claims a method to implement such treatment by the administration of “a composition comprising a therapeutically effective amount of one or more ocular antioxidants.” Claim 2 specifies that the ocular antioxidants of claim 1 be members of the Markush group: “antioxidant vitamins, carotenoids, antioxidant minerals, natural antioxidants extracts and synthetic antioxidants.”

Claims 3–13 all expand upon claim 2, with each claim adding a narrowing limitation to one of the constituent ocular antioxidant groups in claim 2.

Claim 3 specifies that the antioxidant vitamin in claim 2 be “selected from the list consisting of vitamins A, C, and E.” Claim 8 specifies that the “therapeutically effective amount” of the antioxidant vitamins of claim 2 be in the

identified a “general consensus” in the field that hyperopia was a risk factor for developing AMD. Ex. 1003, 3; *see also* Ex. 1004, 10.

range between “0.02 (1 IU) and 15 mg (150 IU) per kilogram of body weight of said subject per day.”

Claim 4 specifies that the carotenoid in claim 2 be “selected from the list consisting of lutein, zeaxanthin, beta-carotene, retinoids, retinal, retinaldehyde, and meso-zeaxanthin.” Claim 9 specifies that the “therapeutically effective amount” of the carotenoid in claim 2 be in the range between “0.0001 and 2 mg per kilogram of body weight of said subject per day.”

Claim 5 specifies that the antioxidant mineral in claim 2 be “selected from the list consisting of zinc, copper, and selenium.” Claim 10 specifies that the “therapeutically effective amount” of the antioxidant mineral in claim 2 be in the range between “0.0001 and 5 mg per kilogram of body weight of said subject per day.”

Claim 6 specifies that the natural extract in claim 2 be “selected from the list consisting of polyphenols, quercetin, anthocyanins, and anthocyanidins.” Claim 12 specifies that the “therapeutically effective amount” of the natural extract in claim 2 be in the range between “0.0001 and 20 mg per kilogram of body weight of said subject per day.”

Claim 7 specifies that the synthetic antioxidant in claim 2 be “selected from the list consisting of BHT, BHA, and BTHQ.” Claim 11 specifies that the “therapeutically effective amount” of the synthetic antioxidant in claim 2 be in the

range between “0.001 and 15 mg per kilogram of body weight of said subject per day,” while claim 13 specifies that this amount be in the range between “0.0001 and 20 mg per kilogram of body weight of said subject per day.”

B. Prosecution History

The Examiner allowed the claims of the '955 Patent only after amendments that: (1) limited the claims to the treatment of subjects having both AMD “and either hyperopia or astigmatism, relative to the age-related macular degeneration in a subject having age-related macular degeneration but neither hyperopia nor astigmatism” and (2) specified “[a] method of treating the increased age-related macular degeneration present.” Ex. 1002, 14–15 (Notice of Allowability).

VI. Level of Ordinary Skill in the Art

Based on the disclosure of the '955 Patent, a person of ordinary skill in the art of the '955 Patent at the time of the alleged invention (“POSA”) “would have been an individual with a Bachelor’s degree in the physical or life sciences (Chemistry, Physics, or Biology) along with at least two years of experience researching ocular disorders.” *See* Ex. 1008, ¶12.

VII. Claim Construction

An unexpired claim in IPR is given its “broadest reasonable construction in light of the specification of the patent in which it appears.” 37 C.F.R. §42.100(b). Claim terms are given their “broadest reasonable construction in light of the specification as they would be interpreted by one of ordinary skill in the art.”

Trivascular, Inc. v. Samuels, 812 F.3d 1056, 1061–62 (Fed. Cir. 2016). Under this standard, the terms of the '955 Patent should be interpreted consistent with their ordinary and customary meaning.

Petitioner does not believe any terms of the '955 Patent require specialized constructions, at least for purposes of the issues in this proceeding, and should be interpreted consistent with their ordinary and customary definition, in accordance with the applicable standard. Petitioner notes that the '955 Patent provides an express definition of “treating,” which is consistent with the ordinary and customary meaning of the term:

As used herein, the terms ‘treated’ and ‘treating’ refers to preventing or delaying the appearance of clinical symptoms of a disease or condition in a subject that may be afflicted with or predisposed to the disease or condition, but does not yet experience or display clinical or subclinical symptoms of the disease or condition. ‘Treating’ also refers to inhibiting the disease or condition, i.e., arresting or reducing its development or at least one clinical or subclinical symptom thereof. ‘Treating’ further refers to relieving the disease or condition, i.e., causing regression of the disease or condition or at least one of its clinical or subclinical symptoms. The benefit to a subject to be treated is either statistically significant or at least perceptible to the subject and/or the physician.

Ex. 1001, 2:43–55.

The '955 Patent also provides an express definition of “therapeutically effective amount,” which is likewise consistent with the term’s ordinary and customary meaning:

As used herein, the term ‘therapeutically effective amount’ refers to the amount/dose of a compound or pharmaceutical composition that is sufficient to produce an effective response (i.e., a biological or medical response of a tissue, system, animal or human sought by a researcher, medical doctor or other clinician) upon administration to a subject.

Ex. 1001, 2:33–42.

VIII. Summary of References Applied in This Petition

Contrary to the assertion in the '955 Patent that “no publications or references have been identified relating [the factors associated with AMD incidence, the effects of light upon the retina, and the effect of ocular antioxidants in helping to reduce the progression of AMD] in a unified manner,” Ex. 1001, 4:28–30, review articles such as Snider (Ex. 1003) and McLaughlan (Ex. 1004) each bring together these points of understanding in a single reference.

As noted in these review articles, which summarize and cite to an array of scholarly publications, numerous clinical studies, including Richer (Ex. 1006), teach the effective treatment of AMD through supplementation with antioxidants such as the carotenoids lutein and zeaxanthin. Moreover, a POSA would have

been aware of studies such as Chaine (Ex. 1005), which identify hyperopia as a risk factor for the development of AMD. *See* Ex. 1003, 6 (citing Richer as reference number 22); Ex. 1004, 12 (citing Chaine as reference number 10).

A. Snider (Ex. 1003)

Snider, the lead reference in this petition, was published in a supplement to the November 2008 issue of *Optometric Management*, a publication that is “dedicated to helping optometrists improve their practice through relevant, actionable and practical columns and features that enhance patient outcomes and bolster the bottom line.” *See Optometric Management*, <http://www.optometricmanagement.com> (last visited 11/15/2016). Snider has been publicly accessible since November 2008, *see* Ex. 1012, and qualifies as prior art under 35 U.S.C. §102(b). Snider was not cited or considered by the Examiner during prosecution of the '955 Patent.

Snider is a review article that summarizes contemporary scholarly development in the treatment of AMD and the available research and literature at the time of its publication. Snider provides a broad discussion of known approaches for the treatment of AMD from the viewpoint of an eye-care practitioner.

As set forth on the front page of Snider, this article is intended to help eye-care practitioners “[I]earn about the pathogenesis of MD [macular degeneration],

how to identify patients at risk and slow its progression through diet and nutritional supplementation.” Ex. 1003, 1. In addition to explaining the state of available AMD treatments, Snider teaches that “[p]reventative care via risk assessment, coupled with effective early intervention, may end the battle against MD that leads to permanent vision loss.” *Id.* at 7. Snider further teaches that “current thinking suggests that ocular changes begin decades before the onset of signs or symptoms [of AMD].” *Id.* at 2. In the context of risk assessment, Snider discusses the “general consensus” classifying hyperopia as one of the “nonmodifiable risk factors” for AMD. *Id.* at 3.

Snider further teaches the need for treatment of oxidative stress to combat development and progression of AMD and discusses several studies involving the treatment of AMD via antioxidant supplementation. *Id.* at 3. Snider highlights the ability of carotenoids to reduce oxidative stress, concluding that “[m]ost likely, the dual action of the dietary carotenoids lutein, zeaxanthin and meso-zeaxanthin represent the 1–2 combination punch for protecting the macula.” *Id.* at 7. Among the studies cited by Snider disclosing the successful treatment of AMD through carotenoid supplementation is Richer (Ex. 1006), which is discussed below. Snider teaches that “[f]or patients with a low MPPD [macular protective pigment density] or a *low average MPPD coupled with other risk factors, practitioners can prescribe an oral supplement that contains all three carotenoids,*” noting that the

“decreased rate of progression” of AMD achieved in previous studies “makes a *very compelling case for placing every patient at any stage of MD on a triple carotenoid supplement.*” *Id.* at 6 (emphasis added).

Snider places particular emphasis on the importance of eye-care practitioners considering certain risk factors, including hyperopia, when devising ocular antioxidant supplementation regimens for patients with AMD. For example, Snider states that “[a]s gatekeepers for vision care, eyecare practitioners can play an important role in preventing vision impairment from AMD and reducing healthcare costs by *proactively screening their patients for risk and taking appropriate measures to reduce that risk.*” *Id.* at 2 (emphasis added). Moreover, Snider teaches that “[t]he eyecare practitioner determines the need for interventional supplementation therapy based on MPPD *and other risk factors for MD the patient may have.*” *Id.* at 6 (emphasis added).

Snider additionally discloses the “effective supplementation” of ocular antioxidants such as carotenoids and lists the lutein, zeaxanthin, and meso-zeaxanthin content in various commercially available daily carotenoid supplements. *See id.* at 6, Table 1. Snider teaches that “[a]pproximately 20 mg of carotenoids per day are needed to effectively repigment the retina.” *Id.* at 6.

Snider also teaches that in addition to carotenoids, “[a] broad spectrum of antioxidants has been indicated as protective of the macula [including] vitamins A,

C and E, alpha-carotene and beta-carotene, L-glutathione and beta-cryptoxanthin[,] . . . zinc, copper and selenium[,] . . . [p]olyphenols and the long-chain omega-3 fatty acids.” *Id.* at 7.

B. McLaughlan (Ex. 1004)

McLaughlan is an article titled “Awareness of Age-related Macular Degeneration and Associated Risk Factors,” which appears in a 2005 report by AMD Alliance International, “a nonprofit coalition of the world’s leading vision, research, and seniors organizations working to raise awareness of age-related macular degeneration (AMD), of treatment and rehabilitation options, and of the importance of early detection.” *See National Eye Institute*, <https://nei.nih.gov/content/amd-alliance-international> (last visited 11/15/2016). McLaughlan has been publicly accessible since September 2005 and thus qualifies as prior art under 35 U.S.C. §102(b).⁴ McLaughlan was not cited or considered by the Examiner during prosecution.

⁴ McLaughlan shows a date of “September 2005” and states that “[t]his report is available to download from our website or in alternative formats upon request.”

Ex. 1004, 24. As further support that McLaughlan qualifies as prior art under 35 U.S.C. §102(b), WIPO International Publication No. WO2007118095 A2, which was published on October 18, 2007, cites to McLaughlan. *See* Ex. 1013, [0035].

McLaughlan aims to spread awareness about AMD by “present[ing] the current understanding of factors that increase the risk of developing AMD and recommendations for preventative measures.” Ex. 1004, 9. Like Snider, McLaughlan reviews the available literature and studies relating to the treatment of AMD at the time of its publication and teaches the need to treat patients at risk for developing AMD.

McLaughlan stresses that “[p]eople need to know if they are at a higher risk of developing AMD so they can focus on avoiding the environmental risk factors that could increase this risk even further.” Ex. 1004, 10 (emphasis added). In particular, McLaughlan (like Snider) identifies hyperopia as one of the “unavoidable factors that increase the risk of developing AMD” and teaches the need for people with hyperopia to take precautionary measures such as “regular eye tests.” *Id.* at 10, 12 (emphasis added). McLaughlan cites the Chaine study (Ex. 1005), discussed below, to support the identification of hyperopia as a risk factor for AMD. *Id.* at 12.

In terms of how to decrease the risk of AMD, McLaughlan emphasizes the benefit of an “overall focus on a healthy lifestyle,” Ex. 1004, 15, but also identifies “[l]ack of nutrients and antioxidants” as one of the specific “environmental factors [for developing AMD] that individuals can control.” *Id.* at 13. McLaughlan notes that “[t]he main supplements discussed in the context of prevention are lutein and

zeaxanthin” and provides an overview of studies showing the beneficial effects of these ocular antioxidants in treating AMD. Ex. 1004, 14 (emphasis added). Like Snider, McLaughlan cites clinical studies teaching that lutein and zeaxanthin “may play a significant role in preventing oxidative damage to the macula, thereby preventing the development of AMD.” *Id.*

C. Chaine (Ex. 1005)

Chaine was published in the September 1998 issue of the *British Journal of Ophthalmology*. Chaine has been publicly accessible since shortly after September 22, 1998, *see* Ex. 1010, 2, and qualifies as prior art under 35 U.S.C. §102(b).

Chaine was not cited or considered by the Examiner during prosecution.

Chaine describes the results of a “case-control study . . . to determine the risk factors for the development of age related macular degeneration (AMD).” Ex. 1005, Abstract. McLaughlan cites Chaine in identifying hyperopia as a risk factor for AMD. Ex. 1004, 12, n.10.

The Chaine study compared AMD-free individuals (controls) with patients having AMD. “The goals of the present study were to further explore the possible link between environmental factors and systemic and ocular conditions that may be risk factors for AMD in a European population.” Ex. 1005, 996. Logistic regression analysis of data collected from study subjects resulted in the identification of hyperopia as one of “six *major risk factors* for AMD.” *Id.*

(emphasis added). Chaine’s study calculated an odds ratio between hyperopia and AMD to be 1.33. *Id.* An odds ratio between properties above 1 (one) signifies a direct statistical association between those properties. Ex. 1008, ¶50. Chaine notes that the recognition of hyperopia as a risk factor for AMD “has been reported previously by several authors” and concludes that “[t]his large case-control study confirms some of the risk factors previously identified and may contribute to the determination of methods for prevention of AMD.” Ex. 1005, 996, 1001.

The ’955 patent asserts that “it must be noted that no clinical study has been conducted to confirm or refute the existence of such a relationship [between hyperopia and AMD].” Ex. 1001, 7:25–27. In direct contrast to this statement, Chaine demonstrated a statistical link between hyperopia and the development of AMD.

D. Richer (Ex. 1006)

Richer was published in the April 2004 issue of *Optometry*, the Journal of the American Optometric Association, and qualifies as prior art under 35 U.S.C. §102(b). Richer has been publicly accessible since shortly after April 12, 2004. *See* Ex. 1011, 2. Richer was cited during prosecution of the ’955 Patent by the Applicant but was not applied by the Examiner to reject any claim. *See* Ex. 1002, 24 (Information Disclosure Statement by Applicant).

Richer is directed to improving visual function in subjects suffering from AMD by supplementation with lutein. Notably, the specification of the '955 Patent cites to Richer, acknowledging that “[m]ultiple studies, particularly the Lutein Antioxidant Supplementation Trial (the LAST Study) conducted by Dr. Stuart Richer have produced results demonstrating that visual acuity, contrast sensitivity, and the amount of macular pigment in the human eye can be improved as a result of lutein and zeaxanthin supplementation or a combination of these xanthophylls with other antioxidants.” *See* Ex. 1001, 4:33–39. Snider also cites Richer as an exemplary study demonstrating the effective use of carotenoids to treat AMD. Ex. 1003, 6.

Richer published the results of the LAST study, which administered lutein supplements as well as other antioxidants to patients suffering from AMD. The study sought to “determine whether nutritional supplementation with lutein or lutein together with antioxidants, vitamins, and minerals, improves visual function and symptoms in atrophic ARMD [age-related macular degeneration].” Ex. 1006, 216. Based on the results of this study, Richer concludes that “visual function is improved with lutein alone or lutein together with other nutrients.” *Id.* Through the beneficial results achieved in AMD patients treated with lutein alone, Richer teaches the effectiveness of a daily “dose of 10-mg non-esterified lutein.” *Id.* at 217. Through the results achieved with lutein combined with other antioxidants,

Richer also teaches effective daily dosages, including “2,500 IU vitamin A . . . 1,500-mg vitamin C . . . 500 IU natural vitamin E . . . 25-mg zinc . . . 1-mg copper . . . 200-mcg selenium . . . 100-mg quercetin.” *Id.* at 217–18.

E. Ciolkowski (Ex. 1007)

United States Patent Application Publication No. US2009/0239836 to Ciolkowski was filed on March 5, 2009 and published on September 24, 2009, *see* Ex. 1007, thus qualifying as prior art under 35 U.S.C. §§102(a) and 102(e). Ciolkowski was not cited or considered by the Examiner during prosecution.

Ciolkowski is directed to various “multifunctional ophthalmic compositions,” *id.* at [0002], which “can be used to treat an ocular disease, disorder, or condition including . . . age macular degeneration,” *id.* at [0076].

In particular, Ciolkowski teaches *anti-oxidants* as “medicaments . . . for use in an ocular environment, *id.* at [0050], and specifically discloses the “*BHT antioxidant*” as a component in several preferred formulations, *id.* at [0092], [0094], [0095], [0097], [0100], [0103] (emphasis added).

IX. The Challenged Claims Are Unpatentable

As set forth in Section IX.B below and in the declaration of Dr. John Landrum (Ex. 1008), the references cited in Grounds I-III render obvious each of claims 1–13 of the ’955 Patent under 35 U.S.C. §103 and provide a reasonable likelihood that the Petitioner will prevail on at least one claim. 35 U.S.C. §314(a).

None of Grounds I-III were considered by the Examiner during prosecution or raised the same prior art that was considered by the Examiner. In addition, the Petition includes the declaration of Dr. Landrum, which was also not before the Examiner. Accordingly, none of Grounds I-III present the same or substantially the same prior art or arguments to the Office. 35 U.S.C. §325(d).

A. Summary of Obviousness Arguments

The '955 Patent acknowledges the connections made in the prior art between AMD, ocular antioxidant supplementation, and hyperopia but nonetheless declares that it is the first reference “relating all of these factors in a unified manner.” Ex. 1001, 4:28–30. Snider proves the contrary.

Through the teachings brought together and reviewed in Snider, a POSA would recognize hyperopia as a risk factor for AMD and understand the need to treat those at risk for developing AMD. *See* Ex. 1008, ¶49. Snider teaches that hyperopia is a “nonmodifiable risk factor” that is “associated with the development of [A]MD,” Ex. 1003, 2, and emphasizes the importance of administering ocular antioxidants to individuals having risk factors for AMD such as hyperopia, stating that “[t]he eye-care practitioner determines the need for interventional supplementation therapy [with ocular antioxidants] based on MPPD and other risk factors for MD the patient may have.” *Id.* In fact, Snider stresses that there is a “very compelling case for placing every patient *at any stage of MD* on a triple

carotenoid supplement.” *Id.* at 6 (emphasis added). A POSA would thus have been motivated to practice the claims of the ’955 Patent to treat individuals having AMD and hyperopia. *See* Ex. 1008, ¶52. Based on the successful treatment of AMD patients using ocular antioxidants in previous studies, a POSA would reasonably have expected such treatment to be successful. *Id.* at ¶53. To the extent that hyperopia or astigmatism result in “increased age-related macular degeneration” (as recited in the claims of the ’955 Patent), a POSA would reasonably expect success in treating the AMD present in such individuals by using specific ocular antioxidants as claimed. *Id.* Snider alone therefore renders obvious claim 1, as well as numerous dependent claims. *Id.* at ¶45.

Claim 2 requires that the ocular antioxidant in claim 1 be “selected from the group consisting of antioxidant vitamins, carotenoids, antioxidant minerals, natural antioxidant extracts and synthetic antioxidants.” Snider teaches the effective treatment of AMD using carotenoids, vitamins, and minerals and therefore renders claim 2 obvious.

Claim 3 requires that the antioxidant vitamin in claim 2 be “selected from the list consisting of vitamins A, C, and E.” Snider teaches the effective treatment of AMD using vitamins A, C, and E and therefore renders claim 3 obvious.

Claim 4 requires that the carotenoid in claim 2 be “selected from the list consisting of lutein, zeaxanthin, beta-carotene, retinoids, retinal, retinaldehyde, and

meso-zeaxanthin.” Snider teaches the effective treatment of AMD using lutein, zeaxanthin, and meso-zeaxanthin and therefore renders claim 4 obvious.

Moreover, a POSA would choose therapeutically effective amounts of carotenoids that fall within the claimed ranges explicitly disclosed in Snider. Snider thus also renders claim 9 obvious.

Claim 5 requires that the antioxidant mineral in claim 2 be “selected from the list consisting of zinc, copper, and selenium.” Snider teaches the effective treatment of AMD using zinc, copper, and selenium and therefore renders claim 5 obvious.

Claim 6 requires that the natural extract in claim 2 be “selected from the list consisting of polyphenols, quercetin, anthocyaninc, and anthocyanidins.” Snider teaches the effective treatment of AMD using polyphenols and therefore renders claim 6 obvious.

As for claims 8, 10, and 12, which recite certain specific therapeutically effective amounts of antioxidant vitamins, antioxidant minerals, and natural antioxidants, although Snider does not specifically disclose such amounts, a POSA would look to clinical studies to find such therapeutically effective amounts. Numerous prior art studies disclose the administration of therapeutically effective amounts of such antioxidants. Richer, in particular, discloses the effective daily administration of (i) the antioxidant vitamins A, C, and E; (ii) the antioxidant

minerals zinc, copper and selenium; and (iii) the natural antioxidant quercetin to subjects with AMD. These amounts fall within the ranges of claims 8, 10, and 12, respectively. Therefore, the combination of Snider and Richer renders those claims obvious.

As for claims 7, 11, and 13, although Snider does not specifically disclose the use of synthetic antioxidants to treat AMD, a POSA motivated to treat the increased AMD in subjects with AMD and hyperopia using ocular antioxidants would understand based on references such as Ciolkowski that BHT, a synthetic antioxidant, was useful in ophthalmic compositions for treating ocular disorders, including AMD. Combining the teachings of Snider and Ciolkowski, a POSA would have been motivated to administer BHT to subjects with AMD and hyperopia. Moreover, Ciolkowski discloses known dosages for BHT as a component in ophthalmic compositions. Therefore, the combination of Snider and Ciolkowski renders claims 7, 11, and 13 obvious.

B. Ground I - Claims 1–6 and 9 of the '955 Patent are unpatentable as obvious over Snider.

- 1. Claim 1 (preamble) - “A method of treating the increased age-related macular degeneration present in a subject having age-related macular degeneration and either hyperopia or astigmatism, relative to the age-related macular degeneration present in a subject having age-related macular degeneration but neither hyperopia nor astigmatism, comprising”**

Snider discloses or suggests this claim element. Snider is a review article summarizing scholarly teachings regarding the treatment of AMD and promoting the known benefits of ocular antioxidants such as carotenoids for reducing the rate of progression for AMD. *See* Ex. 1003. In particular, Snider discloses hyperopia as a “risk factor” for AMD and teaches the need to “take[] appropriate measures to reduce that risk.” *See id.* at 2, 3. Snider further teaches that “[f]or patients with a low MPPD or a low average MPPD *coupled with other risk factors, practitioners can prescribe an oral supplement that contains all three carotenoids.*” *Id.* at 6 (emphasis added). Thus, Snider provides express motivation for treating hyperopic individuals at risk of AMD, and thus for treating any “increased age-related macular degeneration” in such subjects that is attributable to hyperopia, as set forth in claim 1 of the ’955 Patent. Ex. 1008, ¶52.

As an initial matter, the ’955 Patent acknowledges that that the “definite relationship between the ingestion of ocular antioxidants and a reduction in the risk for the incidence and/or progression of AMD” was known in the field. Ex. 1001, 5:7–9. The preamble of claim 1 purports to narrow the application of administration of ocular antioxidants to the treatment of the specific subset of individuals having “increased” AMD who have both AMD and either hyperopia or astigmatism. Therefore, to the extent that this preamble constitutes a limitation on the claims, it would have been obvious to treat any such individuals in the same

way as the general population—i.e., by administering a therapeutically effective amount of ocular antioxidants, as was taught in Snider and well known in the field. *See* Ex. 1003, 6 (“placing every patient at any stage of [A]MD on a triple carotenoid supplement”); *see also* Ex. 1001, 10:30–35 and 5:7–9; Ex. 1006, 217; Ex. 1008, ¶53. Nonetheless, to the extent that there is any question about whether this antioxidant treatment would have been obvious for this specific subset of individuals, Snider provides express motivation for undertaking it.

Snider identifies hyperopia as among the “[n]onmodifiable risk factors” associated with the development of AMD. Ex. 1003, 3. While Snider acknowledges “some conflicting studies” regarding the risk factors associated with the development of AMD, it identifies a “general consensus” supporting the factors identified. *Id.* As further evidence that Snider’s observation regarding hyperopia being a risk factor for AMD was in accordance with the knowledge of a POSA, McLaughlan discusses hyperopia as one of the “unavoidable factors that increase the risk of developing AMD.” Ex. 1004, 12; Ex. 1008, ¶50. McLaughlan in turn cites Chaine, an experimental study wherein “[l]ogistic regression identified” hyperopia as a “major risk factor for AMD (whole population).” Ex. 1004, 12; Ex. 1005, 996; Ex. 1008, ¶50.

Snider additionally teaches the need to treat subjects having risk factors for developing AMD, such as hyperopia. Snider teaches that “[p]reventative care via

risk assessment, coupled with effective early intervention, may end the battle against MD [macular degeneration],” explaining that “ocular changes begin decades before the onset of signs or symptoms [of AMD]” and advising eyecare practitioners to “proactively screen[] their patients for risk and *take[] appropriate measures to reduce that risk.*” Ex. 1003, 7, 2 (emphasis added); Ex. 1008, ¶48. Moreover, Snider teaches that “[t]he eyecare practitioner determines the need for interventional *supplementation therapy* based on MPPD *and other risk factors for MD* the patient may have.” Ex. 1003, 6 (emphasis added).

Specifically, Snider discloses the administration of ocular antioxidants, and specifically carotenoids, as an appropriate measure for treating subjects having risk factors for developing AMD. Ex. 1008, ¶52. As noted above, Snider explicitly teaches that “[f]or patients with a low MPPD [macular protective pigment density] or a low average MPPD coupled with other risk factors, practitioners can prescribe an oral supplement that contains all three carotenoids.” Ex. 1006, 6. Indeed, in a section entitled “Effective Supplementation,” Snider teaches the successful treatment of AMD via ocular antioxidant supplementation, as demonstrated in several clinical studies. *Id.* Snider discusses one particular study concluding that “the dietary intake of carotenoids correlated with a decreased rate of progression for any of the four stages of MD. This makes a *very compelling case* for placing every patient *at any stage* of MD on a triple carotenoid supplement.” *Id.*

(emphasis added). In other words, Snider teaches treating patients with AMD who also have risk factors (including hyperopia) with ocular antioxidants, specifically suggesting treatment of any “increased AMD” attributable to hyperopia. Ex. 1008, ¶52.

That is, by (1) disclosing hyperopia as a risk factor for developing AMD, (2) teaching the need to treat subjects having AMD in combination with risk factors such as hyperopia, and (3) suggesting the administration of ocular antioxidants to treat such increased AMD, Snider provides explicit “teaching, suggestion, or motivation,” under *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), for this claim limitation, i.e., “treating the increased age-related macular degeneration present in a subject having age-related macular degeneration and either hyperopia or astigmatism, relative to the age-related macular degeneration present in a subject having age-related macular degeneration but neither hyperopia nor astigmatism.” Ex. 1001, 12:14–19; Ex. 1008, ¶52.

At a minimum, this claim element is obvious to try in view of Snider because Snider teaches that the administration of carotenoids would be an effective treatment for any stage of AMD. Recognizing that such treatment would be effective for subjects having risk factors for AMD, including hyperopia, a POSA would have had a clear motivation to try such treatment for the “increased AMD” in hyperopic individuals that is attributable to hyperopia, as claimed. *See* Ex.

1008, ¶52. In trying to treat such individuals, a POSA would have selected the solution of administering ocular antioxidants, one of the most widely known and accepted treatment options to “reduce[] the risk of progression of AMD.” *See id.* at ¶25. Moreover, a POSA “would have reasonably expected that dietary supplementation with the carotenoids lutein, zeaxanthin, and meso-zeaxanthin would be effective in treating ‘increased age-related macular degeneration’ in people with hyperopia.” *Id.* at ¶53. Because Snider and the studies discussed therein teach that antioxidant supplementation would be effective in treating “any stage” of AMD, regardless of the cause of the AMD or the presence of other conditions, a POSA would have had a reasonable expectation of success in applying this proven method of treatment to the specific subset of individuals having both AMD and hyperopia, as claimed. *See* Ex. 1003, 6; Ex. 1008, ¶53. Thus, treatment of the increased AMD in subjects with both AMD and hyperopia with ocular antioxidants would have been, at a minimum, obvious to try. *KSR*, 550 U.S. at 414; *see also Hoffmann-La Roche, Inc. v. Apotex, Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) (holding that “conclusive proof of efficacy is not necessary to show obviousness” where prior art suggested “reasonable expectation of success” in using claimed treatment).

2. Claim 1 (body) - “administering to the subject having the macular degeneration and either the hyperopia or astigmatism a composition comprising a therapeutically effective amount of one or more ocular antioxidants.”

Snider expressly discloses this claim element. As discussed above, based on the teaching in Snider, a POSA would have understood hyperopia to be a risk factor for the development of AMD and would have been motivated to administer ocular antioxidants to individuals with AMD and hyperopia, as claimed. Snider teaches that for patients having risk factors for developing AMD such as hyperopia, “practitioners can prescribe an *oral supplement that contains all three carotenoids* [lutein, zeaxanthin, and meso-zeaxanthin].” Ex. 1003, 6 (emphasis added). Snider further states that “[a]long with some key nutrients, it’s the antioxidants and the dual role of the carotenoids serving as both antioxidants and blue light filters, that appear to be the key protectors of healthy vision.” Ex. 1003, 7; Ex. 1008, ¶55. Snider thus discloses the administration of “one or more ocular antioxidants,” as recited in claim 1, by teaching the administration of carotenoids, among other antioxidants. *Id.* at ¶54.

In a section entitled “Effective Supplementation,” Snider references and discusses several studies demonstrating “therapeutically effective amount[s]” of ocular antioxidants in protecting against the development of AMD, including Richer. Ex. 1003, 6. Snider further discloses effective daily dosages for

supplement compositions including lutein, zeaxanthin, and other antioxidants in Table 1, which is reproduced below:

Supplement Breakdown by Macular Protective Pigments Based on Single Tablet/Capsule				
	Lutein	Zeaxanthin	Meso- Zeaxanthin	Total MPP Carotenoids
MacuHealth with LMZ³	10 mg	2 mg	10 mg	22 mg
Zeavision – EyePromise Restore	4 mg	8 mg	0 mg	12 mg
Zeavision – EyePromise Ten	10 mg	0 mg	0 mg	10 mg
Bausch & Lomb – Ocuvite/Lutein	6 mg	0 mg	0 mg	6 mg
Bausch & Lomb – PreserVision	5 mg	0 mg	0 mg	5 mg
Alcon – ICaps AREDS	0 mg	0 mg	0 mg	0 mg
Alcon – ICaps Lutein/Zeaxanthin	2 mg	2 mg	0 mg	4 mg
Alcon – ICaps Lutein/Zea/Omega3	3 mg	3 mg	0 mg	6 mg
AmeriScience – TOZAL	10 mg	0.5 mg	0 mg	10.5 mg
Wyeth – Centrum Silver	.25 mg	0 mg	0 mg	.25 mg
Lange Eyecare & Associates – Fortifeye Complete	10 mg	10 mg	0 mg	20 mg

Table 1. MacuHealth with LMZ³ is the only available triple carotenoid supplement. It contains lutein, zeaxanthin and meso-zeaxanthin and has no known drug interactions, side effects or contraindications.

Id. Thus, Snider expressly teaches the administration of a “*composition comprising a therapeutically effective amount of one or more ocular antioxidants,*” as recited in claim 1, by identifying such effective dosages of multi-carotenoid supplements.

Moreover, as explained in Section IX.B.1, a POSA would be particularly motivated to administer the therapeutically effective amounts of antioxidants to individuals having hyperopia and AMD (i.e., to individuals with “increased age-

related macular degeneration” per claim 1), given that Snider identifies hyperopia as a “[n]onmodifiable risk factor” associated with the development of AMD. Ex. 1003, 3; Ex. 1008, ¶49. A POSA further would have understood that the dosages of ocular antioxidants required for therapeutic efficacy would comprise “effective supplementation,” as taught by Snider, for individuals having AMD in combination with hyperopia, which Snider recognizes as a risk factor for AMD. *See* Ex. 1008, ¶56. As discussed above in Section IX.B.1, Snider and the studies discussed therein teach that antioxidant supplementation would be effective in treating “any stage” of AMD, regardless of the cause of the AMD or the presence of other conditions. *Id.* at ¶53. Thus, Snider provides explicit “teaching, suggestion, or motivation,” under *KSR*, 550 U.S. at 418, to administer to subjects having both AMD and hyperopia “a composition comprising a therapeutically effective amount of one or more ocular antioxidants” as required by claim 1.

3. Claim 2 - “The method of claim 1, wherein said ocular antioxidant is selected from the group consisting of antioxidant vitamins, carotenoids, antioxidant minerals, natural antioxidant extracts and synthetic antioxidants.”

Snider expressly discloses this limitation, which is written in Markush form. Thus, the limitation is met where the prior art discloses any member of the group. *See Fresenius USA, Inc. v. Baxter Int'l, Inc.*, 582 F.3d 1288, 1298 (Fed. Cir. 2009) (“Element (a) is written in Markush form, such that the entire element is disclosed by the prior art if one alternative in the Markush group is in the prior art.”). As

discussed above with respect to claim 1 at Section IX.B.2, Snider teaches the administration of a therapeutically effective amount of ocular antioxidants to subjects with AMD and hyperopia (as claimed), and a POSA would have found it obvious to administer such treatment. *See* Ex. 1008, ¶59. Snider teaches the additional limitation of claim 2 by explicitly disclosing the use of carotenoids for such treatment, among other antioxidant classes. *Id.* at ¶62.

Snider specifically teaches that “the dual action of the dietary *carotenoids* lutein, zeaxanthin and meso-zeaxanthin represent the 1–2 combination punch for protecting the macula.” Ex. 1003, 7 (emphasis added). Moreover, Snider specifically discusses study results wherein carotenoid supplementation reduced the progression of AMD. *Id.* at 6; Ex. 1008, ¶56. According to Snider, these studies “make[] a very compelling case for *placing every patient at any stage of MD on a triple carotenoid supplement.*” Ex. 1003, 6 (emphasis added). As discussed above in Section IX.B.2, a POSA would reasonably expect to successfully practice the elements in claim 1 by administering a therapeutically effective amount of carotenoids because carotenoids had previously proven effective in treating subjects having AMD. *See* Ex. 1008, ¶59. Therefore, a POSA would have been motivated to select carotenoids as the ocular antioxidant of choice when seeking to practice the method of claim 1 and would have had a reasonable expectation of success in administering this treatment. *Id.* at ¶62.

4. **Claim 4 - “The method of claim 2, wherein the carotenoid is selected from the list consisting of lutein, zeaxanthin, beta-carotene, retinoids, retinal, retinaldehyde, and meso-zeaxanthin.”**

Snider expressly discloses this limitation, which contains a Markush group of carotenoids. As discussed above with respect to claim 2 at Section IX.B.3, Snider teaches the administration of a therapeutically effective amount of carotenoids to subjects with AMD and hyperopia, as claimed. Snider teaches the additional limitation of claim 4 by explicitly disclosing the use of lutein, zeaxanthin, and meso-zeaxanthin for such treatment. *See* Ex. 1008, ¶69.

Snider specifically teaches that “the dual action of the dietary carotenoids *lutein, zeaxanthin and meso-zeaxanthin* represent the 1–2 combination punch for protecting the macula.” Ex. 1003, 7 (emphasis added). Snider also teaches that “practitioners can prescribe an oral supplement that contains all three carotenoids [lutein, zeaxanthin, and meso-zeaxanthin]” for patients at risk for developing AMD and that “the dietary intake of carotenoids correlated with a decreased rate of progression for any of the four stages of MD.” Ex. 1003, 6. Therefore, a POSA would have been motivated to select at least three members of the Markush group—lutein, zeaxanthin, and meso-xeaxanthin—as carotenoids of choice when seeking to treat AMD because a POSA would understand that these three macular pigments are the three carotenoids shown by studies to protect against AMD. *See* Ex. 1008, ¶70.

5. Claim 9 - “The method of claim 2, wherein said therapeutically effective amount of said carotenoid is between 0.0001 and 2 mg per kilogram of body weight of said subject per day.”

Snider expressly discloses this limitation. As discussed above with respect to claim 2 at Section IX.B.3, Snider teaches the administration of a therapeutically effective amount of carotenoids to subjects with AMD and hyperopia, as claimed. Snider teaches the additional limitation of claim 9 by explicitly disclosing effective dosages of carotenoids falling within the claimed range. *See* Ex. 1008, ¶82.

Snider teaches that “[a]pproximately 20 mg of carotenoids per day are needed to effectively repigment the macula.” Ex. 1003, 6. The ’955 Patent states that “[t]he amounts described [therein] pertain to a suggested dosage for an individual weighing approximately 150 pounds (approximately 70 kg).” Ex. 1001, 11:46–49. Given a patient subject weight of 70 kilograms, Snider’s teaching corresponds to a “therapeutically effective amount” of 0.29 mg per kilogram of body weight. Ex. 1008, ¶82.

Therefore, Snider discloses dosages falling within the claimed range of a “therapeutically effective amount” of carotenoids. Snider also provides a breakdown of the lutein, zeaxanthin, and meso-zeaxanthin content of 11 different commercially available carotenoid supplements available in 2008, which each contained some combination of carotenoids in amounts varying from 0.25 mg to 10 mg each. *See* Ex. 1003, 6 (Table 1, reproduced above). Each of these dosages,

when converted to milligrams per kilogram of body weight, also falls within the claimed range of “therapeutically effective amount[s].” Moreover, Snider discusses and references multiple studies teaching effective carotenoid supplementation dosages falling within this claimed range, including Richer, which teaches the effectiveness of a daily “dose of 10-mg non-esterified lutein.” Ex. 1006, 217; Ex. 1008, ¶83.

As discussed above with respect to claim 1 at Section IX.B.2, a POSA would have had a reasonable expectation of success in administering the carotenoid dosages disclosed in Snider to patients having both AMD and hyperopia because Snider suggests treating individuals with AMD without restriction as to whether they have any other condition. *See* Ex. 1008, ¶53. A POSA therefore would have been motivated to practice the method of claim 2 by administering dosages of carotenoids falling within the range of “therapeutically effective amount[s]” disclosed in claim 9. Ex. 1008, ¶83.

6. Claim 3 - “The method of claim 2, wherein said antioxidant vitamin is selected from the list consisting of vitamins A, C, and E.”

Snider discloses or suggests this limitation which contains a Markush group of antioxidant vitamins. As discussed above with respect to claim 1 at Section IX.B.2, Snider teaches the administration of a therapeutically effective amount of ocular antioxidants to subjects with AMD and hyperopia, as claimed. Snider

teaches the additional limitation of claim 3 by explicitly disclosing the use of vitamins A, C, and E for such treatment (along with carotenoids and other antioxidants). *See* Ex. 1008, ¶65.

Snider teaches that “[a] broad spectrum of antioxidants has been indicated as protective of the macula [including] *vitamins A, C and E*, alpha-carotene and beta-carotene, L-glutathione and beta-cryptoxanthin. Ex. 1003, 7 (emphasis added); Ex. 1008, ¶66. Snider also discusses research studies investigating “dietary consumption of vitamins A, C, E and carotenoids to determine if any correlation existed between their intake and progression of MD,” Ex. 1003, 6. As further evidence of a POSA’s motivation to administer vitamins A, C and E to individuals with AMD and hyperopia, as claimed, in view of Snider, Snider cites to Richer, wherein supplementation with vitamins A, C, and E improved visual function for subjects with AMD. *See* Ex. 1006; Ex. 1008, ¶67. Moreover, a POSA would have had a reasonable expectation of success treating the specific subset of individuals having both AMD and hyperopia, as claimed, by administering vitamins A, C, and E because Snider and the studies discussed therein teach that antioxidant supplementation would be effective in treating “any stage” of AMD, regardless of the cause of the AMD or the presence of other conditions. *See* Ex. 1003, 6; Ex. 1008, ¶66. Therefore, POSA would have been motivated to select at least three members of the Markush group—vitamins A, C, and E—as antioxidant vitamins of

choice when seeking to treat any “increased” AMD in subjects with hyperopia and AMD, as claimed, and would have reasonably expected such treatment to be successful based on the successful treatment disclosed by studies cited in Snider, including Richer. *See* Ex. 1008, ¶66.

7. Claim 5 - “The method of claim 2, wherein said antioxidant mineral is selected from the list consisting of zinc, copper, and selenium.”

Snider discloses or suggests this limitation which contains a Markush group of antioxidant minerals. As discussed above with respect to claim 1 at Section IX.B.2, Snider teaches the administration of a therapeutically effective amount of ocular antioxidants to subjects with AMD and hyperopia, as claimed. Snider teaches the additional limitation of claim 5 by explicitly disclosing the use of zinc, copper, and selenium for such treatment. *See* Ex. 1008, ¶72.

Snider teaches that in addition to carotenoids and vitamins, “[o]ther nutrients linked to playing a key role in macular health are *zinc, copper, and selenium.*” Ex. 1003, 7 (emphasis added). As further evidence of a POSA’s motivation to administer zinc, copper, and selenium to individuals with AMD and hyperopia in view of Snider, Snider cites to Richer, wherein supplementation with zinc, copper, and selenium improved quality of vision for subjects with AMD. *See* Ex. 1003, 6; Ex. 1006 at 217. Moreover, a POSA would have reasonably expected success treating the specific subset of individuals having both AMD and hyperopia (as

claimed) by administering zinc, copper, and selenium because Snider and the studies discussed therein teach that antioxidant supplementation would be effective in treating “any stage” of AMD, regardless of the cause of the AMD or the presence of other conditions. *See* Ex. 1003, 6; Ex. 1008, ¶75. Therefore, a POSA would have been motivated to select at least three members of the Markush group—zinc, copper, and selenium—as antioxidant minerals of choice when seeking to treat any “increased” AMD in subjects with hyperopia and AMD, as claimed, because a POSA would understand that these antioxidant minerals achieved beneficial results when used to treat AMD in previous studies. Ex. 1008, ¶75.

8. Claim 6 - “The method of claim 2, wherein said natural extract is selected from the list consisting of polyphenols, quercetin, anthocyanins, and anthocyanidins.”

Snider discloses or suggests this limitation, which contains a Markush group of natural extracts. As discussed above with respect to claim 1 at Section IX.B.2, Snider teaches the administration of a therapeutically effective amount of ocular antioxidants to subjects with AMD and hyperopia, as claimed. Snider teaches the additional limitation of claim 6 by explicitly disclosing the use of polyphenols for such treatment. *See* Ex. 1008, ¶77.

In discussing the “broad spectrum of antioxidants [] indicated as protective of the macula,” Snider teaches that “[p]olyphenols and the long-chain omega-3

fatty acids (eicosapentaenoic acid and docosahexaenoic acid) exhibit anti-inflammatory and macular protective qualities.” Ex. 1003, 7 (emphasis added). Snider also cites Richer, wherein supplementation with quercetin (another one of the recited members of the Markush group) improved quality of vision for subjects with AMD. *See* Ex. 1006. Moreover, a POSA would have had a reasonable expectation of success treating the specific subset of individuals having both AMD and hyperopia by administering polyphenols because Snider and the studies discussed therein teach that antioxidant supplementation would be effective in treating “any stage” of AMD, regardless of the cause of the AMD or the presence of other conditions. *See* Ex. 1003, 6; Ex. 1008, ¶79. A POSA would have been motivated to select at least one member of the Markush group—polyphenols—as a natural extract of choice when seeking to treat AMD because a POSA would understand polyphenols to protect against the macular damage leading to AMD. Ex. 1008, ¶79.

C. Ground II - Claims 8, 10, and 12 of the '955 Patent are unpatentable as obvious over the combination of Snider and Richer.

- 1. Claim 8 - “The method of claim 2, wherein said therapeutically effective amount of said antioxidant vitamin is between 0.02 (1 IU) and 15 mg (150 IU) per kilogram of body weight of said subject per day.”**

The combination of Snider and Richer renders obvious this claim. As explained above in Section IX.B.3, Snider alone renders claim 2 obvious. Richer discloses the additional “therapeutically effective amount” limitation of claim 8.

As explained above in Section IX.B.6, a POSA would have been motivated to treat subjects with AMD and hyperopia with at least three antioxidant vitamins—vitamins A, C, and E—based on the teachings of Snider. *See* Ex. 1008, ¶¶66. Although Snider may not directly disclose appropriate dosages for antioxidant vitamins, a POSA would have been motivated to turn to a clinical study such as Richer in order to determine therapeutically effective amounts of antioxidant vitamins for treatment of AMD. *Id.* at ¶86. Snider directly cites Richer as a study demonstrating the effective treatment of AMD. *See* Ex. 1003, 6. Therefore, a POSA would have been motivated to combine Snider and Richer in order to determine “therapeutically effective amount[s]” of antioxidant vitamins to administer to patients with both hyperopia and AMD, as claimed. Ex. 1008, ¶88.

Richer teaches the daily administration of “2,500 IU vitamin A” and “500 IU natural vitamin E” to patients with AMD. Ex. 1006, 217–18. The ’955 Patent states that “[t]he amounts described [therein] pertain to a suggested dosage for an individual weighing approximately 150 pounds (approximately 70 kg).” Ex. 1001, 11:46–49. Given a patient subject weight of 70 kilograms, Snider’s teaching corresponds to a “therapeutically effective amount” of 35.7 IU per kilogram of

body weight per day for vitamin A and 7.14 IU per kilogram of body weight for vitamin E. Ex. 1008, ¶87. Each of these dosages, when converted to milligrams per kilogram of body weight, falls within the claimed range of “therapeutically effective amount[s].” A POSA therefore would have been motivated to practice the method of claim 2 by administering dosages falling within the range of “therapeutically effective amount[s]” disclosed in claim 8. *Id.*

Moreover, a POSA combining the teachings of Snider and Richer to administer dosages of antioxidant vitamins falling within the range of claimed “therapeutically effective amount[s]” would expect to achieve predictable results because such dosages were well known and had proven effective in Richer with respect to subjects having AMD. *Id.* A POSA additionally would expect administration of such dosages to yield the same predictable result in treating any “increased” AMD, as claimed, because as explained above in Section IX.B.6, Snider teaches that the administration of antioxidant vitamins would be effective in treating “any stage” of AMD, regardless of the cause of the AMD or the presence of other conditions. *See* Ex. 1003, 6; Ex. 1008, ¶66. Thus, the method of claim 8 is nothing more than a “combination of familiar elements [from Snider and Richer] according to known methods [to yield] predictable results.” *KSR*, 550 U.S. at 416.

At a minimum, this claim element is obvious to try in view of Snider and Richer. By administering the dosages disclosed in Richer, a POSA would be

choosing from a finite number of known dosages. Moreover, a POSA would have had a reasonable expectation of success because such dosages were well known and had proven effective in Richer with respect to subjects having AMD. Ex. 1008, ¶88. As discussed above with respect to claim 1 at Section IX.B.2, a POSA would have had a reasonable expectation of success in administering these dosages to patients having both AMD and hyperopia because Snider suggests treating individuals with AMD without restriction as to whether they have any other condition. See Ex. 1008, ¶53. Thus, administration of therapeutically effective amounts of antioxidant vitamins within the claimed range to subjects with both AMD and hyperopia would have been, at a minimum, “obvious to try.” See *KSR*, 550 U.S. at 414; *Hoffmann-La Roche*, 748 F.3d at 1332 (claimed dosage was “[a]t the very least . . . obvious to try” where prior art identified a need for claimed dosing regimen and claimed dosage was within a “finite number of identified, predictable solutions.”).

2. Claim 10 - “The method of claim 2, wherein said therapeutically effective amount of said antioxidant mineral is between 0.0001 and 5 mg per kilogram of body weight of said subject per day.”

The combination of Snider and Richer renders obvious this claim. As explained above in Section IX.B.3, Snider alone renders claim 2 obvious. Richer discloses the additional “therapeutically effective amount” limitation of claim 10.

As explained above in Section IX.B.7, a POSA would have been motivated to treat subjects with AMD and hyperopia with at least three antioxidant minerals—zinc, copper, and selenium—based on the teachings of Snider. Ex. 1008, ¶75. Although Snider may not directly disclose appropriate dosages for antioxidant minerals, a POSA would have been motivated to look to a study such as Richer in order to determine therapeutically effective amounts of antioxidant minerals. *See* Ex. 1008, ¶91. Moreover, Snider cites Richer as a study demonstrating the effective treatment of AMD. *Id.* Therefore, a POSA would have been motivated to combine Snider and Richer in order to determine “therapeutically effective amount[s]” of antioxidant minerals to administer to patients with both hyperopia and AMD, as claimed. *Id.*

Richer teaches the daily administration of “25-mg zinc[,], . . . 1-mg copper[, and] . . . 200-mcg selenium” to patients with AMD. Ex. 1006, 218. The ’955 Patent states that “[t]he amounts described [therein] pertain to a suggested dosage for an individual weighing approximately 150 pounds (approximately 70 kg).” Ex. 1001, 11:46–49. Given a patient subject weight of 70 kilograms, Snider’s teaching corresponds to a “therapeutically effective amount” of 3.57 mg per kilogram of body weight per day for zinc, 0.014 mg per kilogram of body weight per day for copper, and 0.003 mg per kilogram of body weight for selenium. Ex. 1008, ¶92. Each of these dosages, when converted to milligrams per kilogram of body weight,

falls within the claimed range of “therapeutically effective amount[s].” *Id.* A POSA therefore would have been motivated to practice the method of claim 2 by administering dosages falling within the range of “therapeutically effective amount[s]” disclosed in claim 10. *Id.* at ¶93.

Moreover, following the reasoning discussed above in Section IX.C.1, a POSA combining the teachings of Snider and Richer to administer dosages of antioxidant minerals falling within the range of claimed “therapeutically effective amount[s]” would expect to achieve predictable results in treating any “increased” AMD in subjects with hyperopia and AMD, as claimed. *Id.* Thus, the method of claim 10 is nothing more than a “combination of familiar elements [from Snider and Richer] according to known methods [to yield] predictable results.” *KSR*, 550 U.S. at 416.

At a minimum, this claim element is obvious to try in view of Snider and Richer. By administering the dosages disclosed in Richer, a POSA would be choosing from a finite number of known dosages. Moreover, a POSA would have had a reasonable expectation of success because such dosages were well known and had proven effective in Richer with respect to subjects having AMD. *Ex.* 1008, ¶93. As discussed above with respect to claim 1 at Section IX.B.2, a POSA would have had a reasonable expectation of success in administering these dosages to patients having both AMD and hyperopia because Snider suggests treating

individuals with AMD without restriction as to whether they have any other condition. Thus, administration of therapeutically effective amounts of antioxidant minerals within the claimed range to subjects with both AMD and hyperopia would have been, at a minimum, “obvious to try.” *See KSR*, 550 U.S. 414; *Hoffmann-La Roche*, 748 F.3d at 1332 (claimed dosage was “[a]t the very least . . . obvious to try” where prior art identified a need for claimed dosing regimen and claimed dosage was within a “finite number of identified, predictable solutions.”).

3. Claim 12 - “The method of claim 2, wherein said therapeutically effective amount of said natural extract is between 0.0001 and 20 mg per kilogram of body weight of said subject per day.”

The combination of Snider and Richer renders obvious this claim. As explained above in Section IX.B.3, Snider alone renders claim 2 obvious. Richer discloses the additional “therapeutically effective amount” limitation of claim 12.

As explained above in Section IX.B.8, a POSA would have been motivated to treat subjects with AMD and hyperopia with natural extracts, including polyphenols, based on the teachings of Snider. *See Ex. 1008*, ¶52. Although Snider may not directly disclose appropriate dosages for natural extracts, a POSA would have been motivated to look to a study such as Richer in order to determine therapeutically effective amounts of natural extracts. *See Ex. 1008*, ¶79.

Moreover, Snider cites Richer as a study demonstrating the effective treatment of AMD. Therefore, a POSA would have been motivated to combine Snider and

Richer in order to determine “therapeutically effective amount[s]” of natural extracts to administer to patients with both hyperopia and AMD, as claimed.

Richer teaches the daily administration of “100-mg quercetin” to patients with AMD. Ex. 1006, 218. Quercetin is “a natural extract and polyphenol.” Ex. 1008, ¶ 97. Claim 6 of the ’955 Patent also includes “quercetin” as a member of the Markush group of natural extracts. *See* Ex. 1001, 12:39. The ’955 Patent states that “[t]he amounts described [therein] pertain to a suggested dosage for an individual weighing approximately 150 pounds (approximately 70 kg).” Ex. 1001, 11:46–49. Given a patient subject weight of 70 kilograms, Snider’s teaching corresponds to a “therapeutically effective amount” of quercetin of 1.43 mg per kilogram of body weight per day. Ex. 1008 ¶97. This dosage, when converted to milligrams per kilogram of body weight, falls within the claimed range of “therapeutically effective amount[s].” *Id.* A POSA therefore would have been motivated to practice the method of claim 2 by administering dosages falling within the range of “therapeutically effective amount[s]” disclosed in claim 12. *Id.* at ¶98.

Moreover, following the reasoning discussed above in Section IX.C.1, a POSA combining the teachings of Snider and Richer to administer dosages of polyphenols falling within the range of claimed “therapeutically effective amount[s]” would expect to achieve predictable results in treating any “increased”

AMD in subjects with hyperopia, as claimed. *Id.* Thus, the method of claim 12 is nothing more than a “combination of familiar elements [from Snider and Richer] according to known methods [to yield] predictable results.” *KSR*, 550 U.S. at 416.

At a minimum, this claim element is obvious to try in view of Snider and Richer. By administering the dosages disclosed in Richer, a POSA would be choosing from a finite number of known dosages. Moreover, a POSA would have had a reasonable expectation of success because such dosages were well known and had proven effective in Richer with respect to subjects having AMD. Ex. 1008, ¶98. As discussed above with respect to claim 1 at Section IX.B.2, a POSA would have had a reasonable expectation of success in administering these dosages to patients having both AMD and hyperopia because Snider suggests treating individuals with AMD without restriction as to whether they have any other condition. Thus, administration of therapeutically effective amounts of natural extracts to subjects with both AMD and hyperopia within the claimed range would have been, at a minimum, “obvious to try.” *See KSR*, 550 U.S. at 414; *Hoffmann-La Roche*, 748 F.3d at 1332 (claimed dosage was “[a]t the very least . . . obvious to try” where prior art identified a need for claimed dosing regimen and claimed dosage was within a “finite number of identified, predictable solutions.”).

D. Ground III - Claims 7, 11, and 13 of the '955 Patent are unpatentable as obvious over the combination of Snider and Ciolkowski.

1. Claim 7 - “The method of claim 2, wherein said synthetic antioxidant is selected from the list consisting of BHT, BHA, and BTHQ.”

The combination of Snider and Ciolkowski renders obvious this claim. As explained above in Section IX.B.3, Snider alone renders claim 2 obvious.

Ciolkowski discloses the additional limitation of claim 7 by explicitly disclosing the administration of the synthetic antioxidant BHT in an ophthalmic formulation. *See* Ex. 1008, ¶101.

As discussed above with respect to claim 1 at Section IX.B.2, Snider teaches or suggests the administration of a therapeutically effective amount of ocular antioxidants to subjects with AMD and hyperopia, as claimed. Further, Snider teaches the benefits of a wide variety of antioxidants for such subjects, as discussed above with respect to claims 4 (carotenoids), 3 (antioxidant vitamins), 5 (antioxidant minerals), and 6 (natural extracts), and references a large body of literature on this subject. Indeed, a POSA would have been aware of other references teaching the treatment of AMD with ocular antioxidants, such as Ciolkowski, which teaches the administration of BHT in ophthalmic compositions useful for treating AMD. Ex. 1008, ¶100.

Ciolkowski is a published patent application directed to “ophthalmic compositions for treatment or control of ophthalmic conditions or disorders” including AMD. Ex. 1007, [0002]. Ciolkowski discloses the inclusion of antioxidants, including BHT, in such ophthalmic compositions. *Id.* at [0050], [0092]. In particular, Ciolkowski discloses ophthalmic compositions comprising “a medicament that has low solubility in water, in an amount such that a therapeutically effective dose of the medicament can be delivered to the eye.” *Id.* at [0012]. Ciolkowski identifies “anti-oxidants” among the “[n]on-limiting examples of medicaments” that can be administered and specifically teaches the inclusion of “BHT antioxidant” in several “examples of compositions of the present invention.” *See id.* at [0050] and [0092–94]. As noted above, Ciolkowski teaches that “[t]he composition can be used to treat an ocular disease, disorder, or condition including . . . age macular degeneration.” *Id.* at [0076]. Therefore, Ciolkowski teaches the administration of BHT in ophthalmic compositions useful for treating AMD. Ex. 1008, ¶101.

Based on the teachings of Ciolkowski and known formulation principles in the field, a POSA would recognize the antioxidant properties of the synthetic antioxidants BHT (Butylated hydroxytoluene), BHA (Butylated hydroxyanisole), and TBHQ (tert-Butylhydroquinone) and their use as common components included in ophthalmic formulations. Ex. 1008, ¶102. Thus, a POSA would have

understood that synthetic antioxidants, as taught in Ciolkowski, would be appropriate to administer to subjects having AMD and hyperopia, as taught in Snider. *Id.*

Moreover, a POSA combining the teachings of Snider and Ciolkowski to administer BHT to treat subjects with hyperopia and AMD would expect such administration to yield predictable results. As discussed above with respect to claim 1 at Section IX.B.2, a POSA would have had a reasonable expectation of success in administering ocular antioxidants to patients having both AMD and hyperopia because Snider suggests treating individuals with AMD without restriction as to whether they have any other condition. *See* Ex. 1008, ¶53. Additionally, a POSA would have understood that administering BHT to patients having both AMD and hyperopia would have predictable results because Ciolkowski suggests treating individuals with AMD without restriction as to whether they have any other risk factors. *See id.* at ¶103. Thus, the method of claim 7 is nothing more than a “combination of familiar elements [from Snider and Ciolkowski] according to known methods [to yield] predictable results.” *KSR*, 550 U.S. at 416.

At a minimum, the additional limitation in claim 7 is obvious to try in view of Snider and Ciolkowski because Ciolkowski teaches the administration of BHT in ophthalmic compositions useful for treating AMD. A POSA would have chosen

BHT from among the finite number of well-known ocular antioxidant options disclosed in Snider and Ciolkowski. A POSA would have had a reasonable expectation of success in administering BHT to patients having both AMD and hyperopia because Ciolkowski suggests treating individuals with AMD without restriction as to whether they have any other condition. *See* Ex. 1008, ¶103. Thus, administration of therapeutically effective amounts of synthetic antioxidants within the claimed range to subjects with both AMD and hyperopia would have been, at a minimum, “obvious to try.” *See KSR*, 550 U.S. 414; *Hoffmann-La Roche*, 748 F.3d at 1332 (claimed dosage was “[a]t the very least . . . obvious to try” where prior art identified a need for claimed dosing regimen and claimed dosage was within a “finite number of identified, predictable solutions.”).

2. Claim 11 - “The method of claim 2, wherein said therapeutically effective amount of said synthetic antioxidant is between 0.001 and 15 mg per kilogram of body weight of said subject per day.”

The combination of Snider and Ciolkowski renders obvious this claim. As explained above in Section IX.B.3, Snider alone renders claim 2 obvious. Ciolkowski discloses the additional “therapeutically effective amount of said synthetic antioxidant” limitation of claim 11. *See* Ex. 1008, ¶106.

As explained above in Section IX.D.1, it would have been obvious to a POSA to combine Snider and Ciolkowski in selecting the synthetic antioxidant BHT to treat subjects with AMD and hyperopia. Ciolkowski further discloses “a

medicament that has low solubility in water, in an amount such that a *therapeutically effective dose* of the medicament can be delivered to the eye,” Ex. 1007, [0012] (emphasis added), additionally and specifically teaches the administration of “one or more drops, one or more times daily” for compositions containing 0.01 grams of BHT per 100 grams of water. *Id.* at [0104]. A POSA would recognize 15 drops to be a typical amount administered daily to treat ophthalmic conditions. Ex. 1008, ¶106. Estimating “one drop” to be 0.05 mL and a daily administration of 15 drops, this equates to a daily dosage of approximately 0.075 mg BHT. *Id.* The ’955 Patent states that “[t]he amounts described [therein] pertain to a suggested dosage for an individual weighing approximately 150 pounds (approximately 70 kg).” Ex. 1001, 11:46–49. Given a patient subject weight of 70 kilograms, Ciolkowski’s teaching corresponds to a “therapeutically effective amount” of BHT of 0.0011 mg per kilogram of body weight per day. Ex. 1008, ¶106. This dosage, when converted to milligrams per kilogram of body weight, falls within the claimed range of “therapeutically effective amount[s].” *Id.* To the extent that the range of amounts claimed in the ’955 Patent is “therapeutically effective,” a POSA would likewise recognize the dosage disclosed in Ciolkowski to be therapeutically effective. *Id.* A POSA therefore would have been motivated to try practicing the method of claim 2 by administering dosages

falling within the range of “therapeutically effective amount[s]” disclosed in claim 11. *Id.*

Moreover, following the reasoning discussed above in Section IX.D.1, a POSA combining the teachings of Snider and Ciolkowski to administer dosages of synthetic antioxidants falling within the range of claimed “therapeutically effective amount[s]” would expect to achieve predictable results in treating subjects with hyperopia and AMD, as claimed. *Id.* Thus, the method of claim 11 is nothing more than a “combination of familiar elements [from Snider and Ciolkowski] according to known methods [to yield] predictable results.” *KSR*, 550 U.S. at 416.

By administering the dosages for BHT disclosed in Ciolkowski, a POSA would be choosing from a finite number of known dosages. A POSA would have had a reasonable expectation of success in administering these dosages to patients having both AMD and hyperopia because Ciolkowski suggests treating individuals with AMD without restriction as to whether they have any other risk factors. *See* Ex. 1008, ¶106. Thus, administration of therapeutically effective amounts of the synthetic antioxidant BHT within the claimed range to subjects with both AMD and hyperopia (as claimed) would have been, at a minimum, “obvious to try.” *See KSR*, 550 U.S. 414; *Hoffmann-La Roche*, 748 F.3d at 1332 (claimed dosage was “[a]t the very least . . . obvious to try” where prior art identified a need for claimed

dosing regimen and claimed dosage was within a “finite number of identified, predictable solutions.”).

3. Claim 13 - “The method of claim 2, wherein said therapeutically effective amount of said synthetic antioxidant is between 0.0001 and 20 mg per kilogram of body weight of said subject per day.”

The combination of Snider and Ciolkowski renders obvious this claim. As explained above in Section IX.B.3, Snider alone renders claim 2 obvious.

Ciolkowski discloses the additional “therapeutically effective amount of said synthetic antioxidant” limitation of claim 13. *See* Ex.1008, ¶109.

As explained above in Section IX.D.1, it would have been obvious to a POSA to combine Snider and Ciolkowski in selecting the synthetic antioxidant BHT to treat subjects with AMD and hyperopia. Ciolkowski further discloses “a medicament that has low solubility in water, in an amount such that a *therapeutically effective dose* of the medicament can be delivered to the eye,” Ex. 1007, [0012] (emphasis added), and specifically teaches the administration of “one or more drops, one or more times daily” for compositions containing 0.01 grams of BHT per 100 grams of water. *Id.* at [0104]. A POSA would recognize 15 drops to be a typical amount administered to treat ophthalmic conditions. Ex. 1008, ¶109. Estimating “one drop” to be 0.05 mL and a daily administration of 15 drops, this equates to a daily dosage of approximately 0.075 mg BHT. *Id.* The ’955 Patent states that “[t]he amounts described [therein] pertain to a suggested dosage for an

individual weighing approximately 150 pounds (approximately 70 kg).” Ex. 1001, 11:46–49. Given a patient subject weight of 70 kilograms, Ciolkowski’s teaching corresponds to a “therapeutically effective amount” of BHT of 0.0011 mg per kilogram of body weight per day. Ex. 1008, ¶109. This dosage, when converted to milligrams per kilogram of body weight, falls within the vast claimed range of “therapeutically effective amount[s].” *Id.* To the extent that the range of amounts claimed in the ’955 Patent is “therapeutically effective,” a POSA would likewise recognize the dosage disclosed in Ciolkowski to be therapeutically effective. *Id.* A POSA therefore would have been motivated to try practicing the method of claim 2 by administering dosages falling within the range of “therapeutically effective amount[s]” disclosed in claim 13. *Id.*

Moreover, following the reasoning discussed above in Section IX.D.1, a POSA combining the teachings of Snider and Ciolkowski to administer dosages of synthetic antioxidants falling within the range of claimed “therapeutically effective amount[s]” would expect to achieve predictable results in treating subjects with hyperopia and AMD. *Id.* Thus, the method of claim 13 is nothing more than a “combination of familiar elements [from Snider and Ciolkowski] according to known methods [to yield] predictable results.” *KSR*, 550 U.S. at 416.

By administering the dosages for BHT disclosed in Ciolkowski, a POSA would be choosing from a finite number of known dosages. A POSA would have

had a reasonable expectation of success in administering these dosages to patients having both AMD and hyperopia because Ciolkowski suggests treating individuals with AMD without restriction as to whether they have any other risk factors. *See* Ex. 1008, ¶110. Thus, administration of therapeutically effective amounts of the synthetic antioxidant BHT within the claimed range to subjects with both AMD and hyperopia would have been, at a minimum, “obvious to try.” *See KSR*, 550 U.S. 414; *Hoffmann-La Roche*, 748 F.3d at 1332 (claimed dosage was “[a]t the very least . . . obvious to try” where prior art identified a need for claimed dosing regimen and claimed dosage was within a “finite number of identified, predictable solutions.”).

X. Conclusion

For the reasons set forth above, *inter partes* review of claims 1–13 of the '955 Patent is requested.

Date: November 21, 2016

Respectfully submitted,

By /David A. Garr/

David A. Garr

Registration No.: 74,932

COVINGTON & BURLING LLP

One CityCenter, 850 Tenth Street, NW

Washington, DC 20001

(202) 662-5250

Jay I. Alexander

Registration No.: 32,678

COVINGTON & BURLING LLP

One CityCenter, 850 Tenth Street, NW

Washington, DC 20001

(202) 662-5622

Attorneys for Petitioner

