

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORMYCON AG.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2025-00233

U.S. Patent No. 11,084,865

**PETITION FOR INTER PARTES REVIEW OF
U.S. PATENT NO. 11,084,865**

DECLARATION OF DR. TODD LEFKOWITZ

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TABLE OF EXHIBITS

Exhibit	Description
1006	Lefkowitz <i>Curriculum Vitae</i>
1009	Hamish M. Fraser et al., Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function, 90(2) J. CLIN. ENDOCRINOL. & METAB. 1114-1122 (Feb. 2005) (“Fraser”)
1011	February 3, 2006 Angiogenesis Presentation (“February 3, 2006 Presentation”)
1012	February 8, 2006 Merrill Lynch Presentation (“February 8, 2006 Presentation”)
1013	March 8, 2006 Lehman Brothers Presentation (“March 8, 2006 Lehman Brothers Presentation”)
1016	Christine Wulff et al., Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2, 143(7) ENDOCRINOLOGY 2797-2807 (Jul. 2002) (“Wulff”)
1018	Chang et al., Practical Approaches to Protein Formulation Development, in Rational Design of Stable Protein Formulations 1 (J.F. Carpenter & M.C. Manning eds., 2002). (“Chang 2002”)
1020	Nayar R, Manning MC. High throughput formulation: strategies for rapid development of stable protein products. Pharm Biotechnol. 2002;13:177-98. (“Nayar”)
1022	September 27, 2005 UBS Global Life Sciences Conference Presentation, https://web.archive.org/web/20051226175624/http://regeneron.com/investor/UBS_Sep05_FF.pdf
1032	AVASTIN®, Approved Labeling, CENTER FOR DRUG EVALUATION AND RESEARCH (2004) (“AVASTIN Label”)
1038	Food & Drug Administration, Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics (May 1999), https://www.fda.gov/media/70788/download . (“FDA Container Closure Guidance”)
1041	Chirila, T.V., Hong, Y. (1998). The Vitreous Humor. In: Black, J., Hastings, G. (eds) Handbook of Biomaterial Properties. Springer, Boston, MA. (“Chirila”)

Exhibit	Description
1042	Silva Tavares Neto JED, Cyrino FVR, Lucena MM, Scott IU, Messias AMV, Jorge R. Intravitreal bevacizumab plus propranolol for neovascular age-related macular degeneration (the BEVALOL study): a phase I clinical trial. <i>Int J Retina Vitreous</i> . 2023. (“Neto”)
1044	Eldeeb M, Chan EW, Dedhia CJ, Mansour A, Chhablani J. One-year outcomes of ziv-aflibercept for macular edema in central retinal vein occlusion. <i>Am J Ophthalmol Case Rep</i> . 2017 Oct 6;8:58-61. (“Eldeeb”)
1045	Macugen Label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021756s006,s007lbl.pdf (“Macugen Label”)
1046	Vitravene Label, https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20961_Vitravene_prntlbl.pdf (“Vitravene Label”)
1048	Vernon SA. Intravitreal triamcinolone therapy for diabetic macular oedema. <i>Br J Ophthalmol</i> . 2005 Aug;89(8):931-3. (“Vernon”)
1049	Jaffe, G.J., Ashton, P., & Pearson, P.A. (Eds.). (2006). <i>Intraocular Drug Delivery</i> (1st ed.). (“Jaffe”)
1050	Rosenfeld PJ, Heier JS, Hantsbarger G, Shams N. Tolerability and efficacy of multiple escalating doses of ranibizumab (Lucentis) for neovascular age-related macular degeneration. <i>Ophthalmology</i> . 2006 Apr;113(4):623.e1. (“Rosenfeld 2006”)
1051	Rosenfeld PJ, Heier JS, Chung CY, McCluskey ER. RhuFab V2 Dose-Escalation Trial: Safety and Tolerability of 3 Escalating Dosing Regimens in Subjects with Age-Related Macular Degeneration (AMD). ASRS Annual Meeting, August 16-20, 2003. (“Rosenfeld 2003”)
1052	Costa RA, Jorge R, Calucci D, Cardillo JA, Melo LA Jr, Scott IU. Intravitreal bevacizumab for choroidal neovascularization caused by AMD (IBeNA Study): results of a phase 1 dose-escalation study. <i>Invest Ophthalmol Vis Sci</i> . 2006 Oct;47(10):4569-78. (“Costa”)
1053	C.A. Cordeiro, R.A. Costa, R. Jorge, D. Calucci, J. Cardillo, I.U. Scott; Intravitreal Bevacizumab for Macular Edema Associated with Hemiretinal and Central Retinal Vein Occlusion . <i>Invest. Ophthalmol. Vis. Sci</i> . 2006;47(13):4257. (“Cordeiro”)

Exhibit	Description
1054	Rosenfeld, Philip J., Andrew A. Moshfeghi, and Carmen A. Puliafito. "Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin®) for neovascular age-related macular degeneration." <i>Ophthalmic Surgery, Lasers and Imaging Retina</i> 36.4 (2005): 331-335. ("Rosenfeld 2005")
1055	Bonini-Filho MA, Jorge R, Barbosa JC, Calucci D, Cardillo JA, Costa RA. Intravitreal injection versus sub-Tenon's infusion of triamcinolone acetonide for refractory diabetic macular edema: a randomized clinical trial. <i>Invest Ophthalmol Vis Sci.</i> 2005 Oct;46(10):3845-9. ("Bonni-Filho")
1056	Gillies MC, Simpson JM, Luo W, Penfold P, Hunyor AB, Chua W, Mitchell P, Billson F. A randomized clinical trial of a single dose of intravitreal triamcinolone acetonide for neovascular age-related macular degeneration: one-year results. <i>Arch Ophthalmol.</i> 2003 May;121(5):667-73. ("Gillies")
1057	Eyetechn Study Group. Anti-vascular endothelial growth factor therapy for subfoveal choroidal neovascularization secondary to age-related macular degeneration: phase II study results. <i>Ophthalmology.</i> 2003 May;110(5):979-86. ("Eyetechn Study")
1058	Hida T, Chandler D, Arena JE, Machemer R. Experimental and clinical observations of the intraocular toxicity of commercial corticosteroid preparations. <i>Am J Ophthalmol.</i> 1986 Feb 15;101(2):190-5. ("Hida")
1059	Jonas JB, Kreissig I, Degenring R. Intraocular pressure after intravitreal injection of triamcinolone acetonide. <i>Br J Ophthalmol.</i> 2003 Jan;87(1):24-7. ("Jonas 2003")
1060	Danis RP, Ciulla TA, Pratt LM, Anliker W. Intravitreal triamcinolone acetonide in exudative age-related macular degeneration. <i>Retina.</i> 2000. ("Danis")
1061	Young S, Larkin G, Branley M, Lightman S. Safety and efficacy of intravitreal triamcinolone for cystoid macular oedema in uveitis. <i>Clin Exp Ophthalmol.</i> 2001 Feb;29(1):2-6. ("Young")
1062	Kenalog Label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/014901s034lbl.pdf ("Kenalog Label")

Exhibit	Description
1063	Jonas JB, Kreissig I, Degenring R. Intravitreal triamcinolone acetonide for treatment of intraocular proliferative, exudative, and neovascular diseases. Prog Retin Eye Res. 2005 Sep;24(5):587-611. (“Jonas 2005”)
1064	Gallemore RP, and Boyer DS. Intravitreal Kenalog Injections, https://www.aao.org/eyenet/article/intravitreal-kenalog-injections (“Gallemore”)
1065	Kuppersmann BD, Thomas EL, de Smet MD, Grillone LR; Vitrase for Vitreous Hemorrhage Study Groups. Safety results of two phase III trials of an intravitreal injection of highly purified ovine hyaluronidase (Vitrax) for the management of vitreous hemorrhage. Am J Ophthalmol. 2005 Oct;140(4):585-97. (“Kuppersmann I”)
1066	Kuppersmann BD, Thomas EL, de Smet MD, Grillone LR; Vitrase for Vitreous Hemorrhage Study Groups. Pooled efficacy results from two multinational randomized controlled clinical trials of a single intravitreal injection of highly purified ovine hyaluronidase (Vitrax) for the management of vitreous hemorrhage. Am J Ophthalmol. 2005 Oct;140(4):573-84. (“Kuppersmann II”)
1067	Vitrax Label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21640s002_003lbl.pdf (“Vitrax Label”)
1068	Gaudreault J, Fei D, Rusit J, Suboc P, Shiu V. Preclinical pharmacokinetics of Ranibizumab (rhuFabV2) after a single intravitreal administration. Invest Ophthalmol Vis Sci. 2005 Feb;46(2):726-33. (“Gaudreault”)
1069	Lucentis Label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/125156lbl.pdf (“Lucentis Label”)
1070	Macugen Drug Approval Letter, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-756_Macugen_approv.pdf (“Macugen Approval Letter”)
1071	CATT Research Group; Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011 May 19;364(20):1897-908. (“CATT Study”)

Exhibit	Description
1072	Oliveira LB, Tatebayashi M, Mahmoud TH, Blackmon SM, Wong F, McCuen BW 2nd. Dispace facilitates posterior vitreous detachment during vitrectomy in young pigs. <i>Retina</i> . 2001;21(4):324-31. (“Oliveira”)
1073	Wang F, Wang Z, Sun X, Wang F, Xu X, Zhang X. Safety and efficacy of dispace and plasmin in pharmacologic vitreolysis. <i>Invest Ophthalmol Vis Sci</i> . 2004 Sep;45(9):3286-90. doi: 10.1167/iovs.04-0026. (“Wang”)
1074	Tezel TH, Del Priore LV, Kaplan HJ. Posterior vitreous detachment with dispace. <i>Retina</i> . 1998;18(1):7-15. (“Tezel”)
1075	Tsui I, Pan CK, Rahimy E, Schwartz SD. Ocriplasmin for vitreoretinal diseases. <i>J Biomed Biotechnol</i> . 2012;2012:354979. (“Tsui”)
1076	Sakuma T, Tanaka M, Mizota A, Inoue J, Pakola S. Safety of in vivo pharmacologic vitreolysis with recombinant microplasmin in rabbit eyes. <i>Invest Ophthalmol Vis Sci</i> . 2005 Sep;46(9):3295-9. (“Sakuma”)
1077	Gandorfer A, Rohleder M, Sethi C, Eckle D, Welge-Lüssen U, Kampik A, Luthert P, Charteris D. Posterior vitreous detachment induced by microplasmin. <i>Invest Ophthalmol Vis Sci</i> . 2004 Feb;45(2):641-7. (“Gandorfer”)
1078	Malik D, Tarek M, Caceres del Carpio J, Ramirez C, Boyer D, Kenney MC, Kuppermann BD. Safety profiles of anti-VEGF drugs: bevacizumab, ranibizumab, aflibercept and ziv-aflibercept on human retinal pigment epithelium cells in culture. <i>Br J Ophthalmol</i> . 2014 Jun;98 Suppl 1(Suppl 1):i11-16. (“Malik”)
1094	Jager RD, Aiello LP, Patel SC, Cunningham ET Jr. Risks of intravitreal injection: a comprehensive review. <i>Retina</i> . 2004 Oct;24(5):676-98. (“Jager”)
1095	Garcia-Valldecabres M, López-Aleman A, Refojo MF. pH stability of ophthalmic solutions. <i>Optometry</i> . 2004 Mar;75(3):161-8. (“Garcia-Valldecabres”)

I. INTRODUCTION

1. I have been retained by Fish & Richardson on behalf of Formycon AG (“Petitioner”) to provide expert opinions regarding intravitreal drugs used in ophthalmology, focusing on their composition and general safety considerations associated such ophthalmic formulations.

2. My opinions in this declaration are based on the documents I cite along with my professional training, experience and knowledge that I have acquired working in the field of ophthalmology over the past 40 years. I am being compensated for my services as an expert at my standard consulting rate of \$500 per hour. My compensation is in no way contingent on the substance of my opinions or the outcome of this case.

3. My opinions and their underlying reasoning are explained in detail below.

II. BACKGROUND AND QUALIFICATIONS

4. I am an ophthalmologist with over 40 years of experience in the research, diagnosis, treatment, and analysis of vitreoretinal eye disorders. I received a Bachelor of Arts degree in Biology from Queens College in 1973. I obtained my M.D. from New York University School of Medicine in 1977. I completed my ophthalmology residency at Georgetown University (1978-1981).

I was certified by the American Board of Ophthalmology in 1982.

5. From 1981 to 1983, I was Chief of Ophthalmology at Scott Air Force Base in Illinois, and from 1983 to 1985, I held the same position at Luke Air Force Base in Arizona. I have been involved in active clinical ophthalmology practices in Arizona and Connecticut from 1981 to 2021.

6. I am currently Locum Tenens at Carondelet St. Joseph's Medical Center in Tucson, Arizona. I joined the faculty at the University of Arizona Medical School / Phoenix Sonoran Desert IME in 2019.

7. In my current and prior positions, I have been involved in the teaching and training of medical students, fellows, and residents in the area of ophthalmological surgical techniques, including specifically, injection protocols for the administration of therapeutics for the treatment of age-related macular degeneration (AMD) and other vitreoretinal eye disorders.

8. I was and/or currently am a member in several Professional and Academic Societies, including American Academy of Ophthalmology, the American Society of Cataract and Refractive Surgeons, the European Society of Cataract and Refractive Surgeons, and the American College of Surgeons, among others.

9. My clinical practice is focused on the diagnosis and treatment of patients suffering from all diseases of the retina, including age-related macular

degeneration, diabetic retinopathy, diabetic macular edema, and related disorders, as well as uveitis. I have experience with surgical interventions as well as the prescription and administration of various intravitreally-administered agents. I routinely administered intravitreal agents as part of my practice.

10. In sum, I have over 40 years of hands-on clinical and research experience specializing in treating vitreoretinal disorders and the prescription, and intravitreal administration. I have included a copy of my *curriculum vitae* in support of my opinions. Ex.1006, Lefkowitz CV.

III. INFORMATION RELIED UPON

13. In addition to my general knowledge gained as a result of my education and experience as an ophthalmologist, I have reviewed and considered, among other things, the prior art of record discussed herein.

14. The full list of information, in addition to my professional, academic and clinical experience, that I have relied upon in forming my opinions for this report is set forth throughout the report and in the Table of Exhibits.

15. Where my conclusions are based on certain assumptions that I have adopted, I have stated such assumptions in this Declaration.

IV. KEY CONSIDERATIONS IN THE FORMULATION OF INTRAVITREAL INJECTIONS AS OF MARCH 2006

16. I provide my opinions below from the standpoint of someone who would evaluate an intravitreal injection for the purposes of administering it to a

patient on or around March 2006, though the considerations below were applicable both before and after that date. I have routinely evaluated intravitreal injections for suitability for administration to a patient in my career as part of prescribing new and existing intravitreal injections to patients.

17. The formulation of intravitreal injections requires attention to several key factors to ensure a patient's safety. Given the eye's vulnerability to infection and injury, ophthalmologists must consider, among other things, sterility, osmolality, dosing concentration, and injection volume.¹ I provide below an overview of these considerations from an ophthalmologist's perspective.

A. Sterility

18. Ensuring sterility is paramount in the formulation of intravitreal injections, as even minimal contamination can result in severe complications, such as endophthalmitis, potentially leading to vision loss. To minimize the risk of infection, medications are prepared in sterile manufacturing environment (or compounding pharmacies) with preservative-free formulations and filtration to eliminate particulates. Strict adherence to safety protocols during administration, including the use of sterile gloves, masks, drapes, and povidone-iodine for ocular

¹ While I am not a formulator, I have extensive knowledge and experience in administering intravitreal drugs from my ophthalmology practice and understand the key factors that affect the clinical outcomes of intravitreal administration.

surface preparation, is essential for minimizing complications and ensuring patient safety during and following intravitreal injections.

B. Osmolality and Tonicity

19. Osmolality and tonicity are critical factors in formulating medications for intravitreal injections. Osmolality refers to the total concentration of solutes in a solution (osmoles/kg), osmolarity refers to osmoles/liter,² while tonicity addresses how those solutes affect water movement across cell membranes, considering only non-penetrating solutes. Osmolality and tonicity are interconnected; both work together to ensure that the solute concentration is balanced with the tissue fluids, maintaining homeostasis and preventing unwanted water movement across cell membranes.

20. An intravitreal formulation should ideally be iso-osmotic, meaning its total solute concentration closely matches that of the eye's natural fluids, to reduce the risk of complications. If the osmolality is too high (hyperosmotic), it can draw water out of cells, leading to dehydration, cell shrinkage, and tissue damage to delicate ocular structures like the retina. Conversely, if the osmolality is too low (hypo-osmotic), water may enter the cells, causing them to swell and potentially

² For dilute aqueous solutions, such as the vitreous cavity, osmolality and osmolarity are approximately the same because the density of water is close to 1 kg/L.

rupture.³

21. Another reason for matching osmolality in intravitreal injections is to minimize patient discomfort. In my experience, patients frequently report noticing differences in concentration gradients when the drug is injected into the eye, and an osmolality imbalance can exacerbate irritation, visual disturbances, and other adverse reactions. In more severe cases, osmolality differences may cause osmotic stress, potentially compromising the structural integrity of ocular tissues and diminishing the treatment's efficacy as noted above. Ensuring that the solution's osmolality is appropriately matched with ocular fluids not only improves patient comfort but also helps preserve the eye's physiological balance, reducing the risk of side effects and complications.

22. Because maintaining proper osmolality is important in ensuring the safety and comfort of intravitreal injections as noted above, intravitreal drug products are typically formulated to match the osmolality of the vitreous humor at around 288-323 mOsm/kg. *See, e.g.,* Ex.1041, Chirila, 126 (listing osmolality of

³ Similarly, if the solution is hypertonic, it can cause water to leave the cells, resulting in cell shrinkage and potential damage. If the solution is hypotonic, it can cause water to enter the cells, leading to swelling and possible rupture. Therefore, for the same reasons iso-osmolality is desired, isotonicity is critical to preventing adverse reactions and ensure the safety and comfort of the patient.

human vitreous body as 288-323 mOsm/kg). For instance, anti-VEGF agents like Macugen, and Eylea, and Avastin were all formulated with an osmolality closely aligned with this range to ensure compatibility with the eye's environment and prevent adverse reactions following injection. Below is a summary table of the known osmolality of each of these anti-VEGF agents as well as other intravitreal drugs.

Intravitreal Drug	Osmolality (mOsm/kg)
Bevacizumab (Avastin)	342
Aflibercept (Eylea)	300
Pegatanib Sodium (Macugen)	280-360
Fomivirsen Sodium (Vitravene)	290
Triamcinolone acetonide (Kenalog)	320

See, e.g., Ex.1042, Neto, 3; Ex.1044, Eldeeb, 60; Ex.1045, Macugen Label, 4; Ex.1046, Vitravene Label, 3; Ex.1058, Hida, 191; Ex.1078, Malik.

C. Volume and Concentration of Injection

23. The volume and concentration of the intravitreal injection must likewise be carefully controlled. Intravitreal injections are typically administered in small volumes ranging from 0.05 to 0.1 ml to minimize complications such as elevated intraocular pressure, which can result in impaired ophthalmic artery perfusion, acute glaucoma, and optic nerve damage. Specifically, by March 2006, it was known that “0.1 ml is the maximum volume most eyes can tolerate when injected into the vitreous cavity without causing inevitable central retinal artery occlusion...” Ex.1048, SA Vernon, 932. Thus, “intravitreal injection of a small

volume (such as 0.10 mL or less) represent[ed] a much more reasonable approach for drug administration.” Ex.1049, Jaffe, 106. 0.1 ml injections were the most commonly injected volume, as shown in the table below.

24. Similarly, a concentration of 40 mg/mL was generally accepted as the maximum tolerated limit for intravitreal injections for ensuring patient safety. Concentrations exceeding this threshold were generally not administered as the small volume of the vitreous cavity limits its capacity to evenly disperse highly concentrated solutions, increasing the risk of localized retinal toxicity.

25. Indeed, approved intravitreal drugs and clinical trials as of March 2006 confirm that the standard maximum injection volume for intravitreal injections is 0.1 mL, with a maximum concentration of 40 mg/mL. While volumes and concentrations above this may have been acceptable in some instances, these were generally regarded as safe maximums:

Drug Agent	Dosing Amount	Dosing Volume	Dosing Concentration
Ranibizumab (Lucentis) ⁴	0.3 mg - 2.0 mg	0.05 mL	6 mg/ml – 40 mg/ml
Bevacizumab (Avastin) ⁵	1.0, 1.5, and 2.0 mg	0.04, 0.06, and 0.08 mL	25 mg/ml
Triamcinolone acetonide (Kenalog) ⁶	4 mg	0.1 ml	40 mg/ml
Pegatanib Sodium (Macugen) ⁷	3 mg	0.1 mL	30 mg/mL

26. A POSA would have particularly been motivated to use the established safe maximum concentration in an intravitreal injection to lengthen the time between any repeat injections. Intravitreal injections were understood to carry significant risks at the time, including the risk of endophthalmitis, a severe and potentially blinding condition. See generally, Ex.1094. Given the known risks of intravitreal injections, a POSA would have been motivated to reduce the number of injections required for the patient. By administering a higher concentration, a POSA would have anticipated the potential to extend the interval between reinjections, thereby reducing the overall injection frequency.

⁴ See, e.g., Ex.1050, Rosenfeld 2006; *see also*, Ex.1051, Rosenfeld 2003.

⁵ See, e.g., Ex.1052, Costa; *see also*, Ex.1053, Cordeiro; Ex.1054, Rosenfeld 2005.

⁶ See, e.g., Ex.1048, Vernon; Ex.1055, Bonini-Filho; Ex.1056, Gillies.

⁷ See, e.g., Ex.1057, Eyetech Study, 3.

D. Biocompatibility

27. Lastly, biocompatibility is important. The formulation must be free of preservatives or excipients that could provoke an immune response or cause toxicity to retinal cells. For example, Macugen is a preservative-free solution designed to be compatible with retinal tissues, minimizing the risk of irritation or inflammation after injection. Ex.1045, Macugen Label, 1.

28. These considerations, ranging from the formulation characteristics to the biocompatibility of the drug, are fundamental to the safe and effective use of intravitreal injections in treating retinal diseases. By carefully understanding each of these factors, ophthalmologists ensure that the treatments they provide are both safe and tailored to the specific needs of the eye.

II. COMPOSITIONS OF PRIOR INTRAVITREAL FORMULATIONS

29. I was also asked to provide an overview of intravitreal formulations available before March 21, 2006, including their approval dates, uses, and compositions. A brief summary is presented below.

30. Triamcinolone acetonide (Kenalog) was initially FDA-approved in 1957 as an injectable corticosteroid for various inflammatory conditions but began being used intravitreally off-label in the late 1990s to manage retinal diseases due to its potent anti-inflammatory effects. It gained widespread use for treating conditions such as diabetic macular edema, uveitis, and macular edema secondary

to retinal vein occlusions.

31. For example, preclinical work by Hida supported intravitreal triamcinolone use in animal models. Ex.1058, Hida. Other studies, including those by Jonas (Ex.1059), Danis (Ex.1060), and Young (Ex.1061) further supported its clinical use. Higher doses, such as 25 mg compounded in 0.2 mL of Ringer's lactate, were also explored. *See, e.g.*, Ex.1059, 1. The standard formulation of Kenalog used for intravitreal injections was a sterile suspension of 40 mg/mL with sodium chloride for isotonicity, 0.99% (w/v) benzyl alcohol as a preservative, 0.75% carboxymethylcellulose sodium, and 0.04% polysorbate 80. Ex.1062, Kenalog Label. Subsequent in vitro studies showed that benzyl alcohol at concentrations modestly higher than what is present in commercial Kenalog, may be toxic to the retinal pigment epithelium of the eye. *See, e.g.*, Ex.1063, Jonas 2005, 604-605; Ex.1064, Gallemore. They suggested that if commercial preserved Kenalog is to be used clinically decanting or other means to remove the benzyl alcohol should be considered. *Id.* For intravitreal injections, doses of up to 4 mg (0.1 ml) were typically administered in small aliquots. Kenalog was used off-label as an intravitreal drug and never received FDA approval for this use.

32. Hyaluronidase (Vitrace®) began being used intravitreally in the early 2000s, primarily for treating vitreous hemorrhage. Vitrace received FDA approval in 2003 for clearing vitreous hemorrhage, but was never officially approved for

intravitreal use. Kuppermann (Ex.1065-66) reported on the use of 7.5 IU, 55 IU, and 75 IU of ovine hyaluronidase, equivalent to 9.3, 68, and 93 USP units, respectively. Vitrase was supplied as a sterile, non-preserved, colorless solution with a pH of 6.4 to 7.2. Each mL of Vitrase contained 200 USP units of ovine hyaluronidase with 0.93 mg lactose, 0.36 mg potassium phosphate dibasic, 0.23 mg potassium phosphate monobasic, and 9.0 mg sodium chloride. Ex.1067, Vitrase Label.

33. Ranibizumab (Lucentis) started being studied for intravitreal use in the early 2000s. Ranibizumab is a monoclonal antibody fragment (rhuFabV2) targeting VEGF, and was studied by Gaudreault (Ex.1068) for intravitreal use. Ranibizumab received FDA approval in 2006 for treating neovascular (wet) AMD.

34. Lucentis comes in a sterile, colorless to pale yellow solution in a single-use glass vial, designed to deliver 0.05 ml of 10 mg/ml ranibizumab in a buffered aqueous solution with 10 mM histidine HCl, 10% a, a-trehalose dihydrate, 0.01% polysorbate 20, pH 5.5. Ex.1069, Lucentis Label, 4.

35. Pegaptanib sodium (Macugen) was first used intravitreally in clinical trials in the early 2000s as one of the earliest anti-VEGF agents approved for ocular use. It was formulated as a 3.47 mg/mL sterile solution in a pre-filled syringe, with a typical dose of 0.3 mg administered intravitreally in 90 µL. Ex.1045, Macugen Label, 1. Macugen had an osmolality of 280–360 mOsm/kg and

a pH of 6–7. *Id.*, 2. It was FDA-approved in December 2004 for the treatment of wet AMD. Ex.1070. The composition used for administration contained 0.3 mg/90 µL of Macugen in a sterile solution of sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, hydrochloric acid, and/or sodium hydroxide to adjust the pH and water for injection. Ex.1045, 1.

36. Bevacizumab (Avastin) was initially FDA-approved in 2004 for metastatic colorectal cancer but started being used intravitreally off-label in 2005 due to its similar mechanism of action to ranibizumab and its significantly lower cost. It was widely adopted for intravitreal injections to treat retinal conditions such as AMD, diabetic macular edema, and retinal vein occlusions. Although not originally intended for ocular use, bevacizumab became widely used in ophthalmology due to its low cost and effectiveness. Each mL of intravenous bevacizumab contains 25 mg bevacizumab, α,α -trehalose dihydrate, polysorbate 20, sodium phosphate dibasic, anhydrous, sodium phosphate monobasic, monohydrate,⁸ and Water for Injection, USP with a pH of 6.2. Ex.1032, Avastin Label. For intravitreal injections, the same formulation (25 mg/ml) was used except that it was injected as 1-1.25 mg (0.04-0.05 ml) aliquots. Ex.1054, 334. Studies

⁸ In addition to phosphate buffers, citrate buffers had been used in intravitreal formulations. *See, e.g.*, Ex.1058, Hida, 191; Ex.1095, Garcia-Valldecabres.

such as the CATT trial demonstrated that its efficacy in treating retinal diseases was comparable to ranibizumab, despite concerns over sterility and consistency due to the repackaging process. Ex.1071, CATT Study.⁹

37. In conclusion, the development and use of intravitreal formulations prior to 2006 provided essential treatments for retinal diseases. Triamcinolone acetonide (Kelalog), hyaluronidase (Vitrase), pegaptanib sodium (Macugen), ranibizumab (Lucentis), bevacizumab (Avastin), and other agents like Dispace and Ocriplasmin played an important role in treating conditions such as AMD, diabetic macular edema, and vitreomacular traction. They laid the foundation for current ophthalmic treatments and established intravitreal injections as a standard practice in clinical care.

III. PRESENTATIONS OF INTRAVITREAL FORMULATIONS

38. Pharmaceutical formulations may be presented (i.e., packaged or supplied) in different ways. In particular, there were two known presentations for intravitreal formulations at the time – a vial and a PFS. *See, e.g.*, Ex.1018, Chang 2002.

39. For intravitreal use, a vial typically contains the medication sealed with

⁹ Several other agents were also explored for intravitreal use before 2006, including Dispace enzyme, and Ocriplasmin (microplasmin). Ex.1072, Oliviera; Ex.1073, Wang; Ex.1074, Tezel; Ex.1075, Tsui; Ex.1076, Sakuma 2005; Ex.1077, Gandorfer.

a synthetic rubber stopper, which is pierced by a syringe to withdraw the appropriate dose. This method is common due to its ease of development and familiarity in clinical settings. In its Container Closure Guidance, published in 1999, FDA specifically recommended that injectable formulations be packaged in vials, among other presentations. Ex.1038, Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics.

40. A pre-filled syringe (PFS) is a syringe pre-loaded with medication, eliminating the need to withdraw it from a vial. This approach offers several advantages, including: (1) ease of use, allowing for potential self-administration or administration without additional handling of the primary container, (2) reduced risk of medication errors and infection, (3) product differentiation, (4) less medication overfill, and (5) compatibility with autoinjectors (for PFSs with a staked-in needle). These benefits make PFSs more commercially desirable.

41. Nayar, titled “High Throughput Formulation: Strategies for Rapid Development of Stable Protein Products, and was published in Rational Design of Stable Protein Formulations” 177, 183 (J.F. Carpenter & M.C. Manning eds., 2002) (“Nayar 2002”), explains that each dosage form “offers various advantages and disadvantages, in the speed of development, manufacturing, packaging and shipment logistics, and in administration of the product to the patient.” Ex.1020, 183. It also explains that the “most preferred” dosage form for a therapeutic protein

product was “a solution formulation that is typically stored in the refrigerator and preferably in a pre-filled syringe.” *Id.*

42. As of the priority date, there were two approved intravitreal preparations. Macugen was supplied in a PFS, and Vitravene was supplied in a vial. Exs.1045-1046. Similarly, Chang 2002 lists “Vial/stoppers” and PFSs as options for “Container/closure” systems. Ex.1018, 4.

IV. DEVELOPMENT OF AFLIBERCEPT

43. Aflibercept (VEGF Trap), a soluble decoy protein with the ability to bind to vascular endothelial growth factor, was investigated for both intravenous and intravitreal applications, targeting conditions driven by abnormal angiogenesis. While intravenous studies focused on systemic effects, particularly on ovarian and thecal angiogenesis, intravitreal applications were simultaneously being investigated for the treatment of retinal diseases like wet age-related macular degeneration (AMD).

44. For instance, Fraser’s study, titled “Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function,” was published in *The Journal of Clinical Endocrinology & Metabolism* in November 2004, prior to the priority date of the ‘865 patent in March 2006. Ex.1009, Fraser. Fraser evaluated VEGF Trap’s impact on ovarian angiogenesis using a formulation that included

excipients similar to those found in the claims of the '865 patent. The formulation contained 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% polysorbate 20 (Tween 20), with either 20% glycerol or 20% sucrose. *Id.*, 2.

45. Similarly, Wulff's study, titled "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2," published in *Endocrinology* in July 2002, also prior to the priority date, confirmed VEGF Trap's efficacy in inhibiting thecal angiogenesis. Ex.1016, Wulff. Like Fraser, the formulation contained 5 mM phosphate, 5 mM citrate, 100 mM NaCl, and 0.1% polysorbate 20 (Tween 20), with 20% sucrose (wt/vol). Wulff's research demonstrated that inhibiting VEGF could prevent blood vessel development in systemic settings. *Id.*, 2.

46. I note that while the formulation disclosed in Fraser and Wulff was intended for intravenous administration, the excipients included in the formulation were commonly used in other intravitreal formulations known at the time, and an ophthalmologist would not have had any reason to be concerned about their suitability for intravitreal injection. *See* Section V. Thus, so long as the Fraser/Wulff formulation was modified such that other considerations for intravitreal injections, including osmolality and volume, are appropriately addressed, a POSA would have understood the modified Fraser/Wulff formulation

would be suitable for intravitreal administration.

47. In fact, by March 2006, a formulation of aflibercept had already demonstrated efficacy when administered intravitreally. For example, Regeneron delivered a series of presentations on February 3, February 8, and March 8, 2006, reporting on the success of aflibercept's intravitreal use in treating wet AMD. Exs.1011-1013. These presentations disclosed that aflibercept formulated for intravitreal use could offer "greater efficacy" and "greater patient convenience/safety" compared to other treatments. *Id.* They highlighted that a single intravitreal injection of aflibercept showed a "[r]apid, substantial, and prolonged (up to at least 4 weeks) reduction in retinal thickness," a desirable clinical outcome for treating wet AMD. *Id.* The presentations also reported that doses ranging from 0.05 to 4.0 mg were being tested in patients, with the February 3, 2006, presentation noting that the "maximum tolerated dose has not yet been reached" and that there were "no ocular serious adverse events". *Id.*

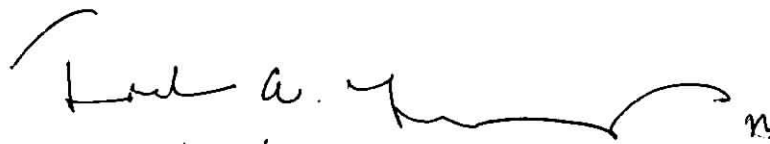
48. By March 8, 2006, Regeneron confirmed that the 4.0 mg dose had been completed, showing evidence of biological activity in reducing retinal thickness without causing safety issues. Ex.1013, 22. A POSA would have understood from this disclosure that the 4 mg dose was safe and effective and would have been motivated to use it. These early clinical trials established the safety and efficacy of aflibercept for intravitreal administration, including a mg

dose of aflibercept, leading to the initiation of Phase 2 trials with a Phase 3 trial the following year. Ex.1013, 24.

V. CONCLUSION

49. This declaration, along with the attached appendices, is based on my present assessment of material and information currently available to me.

50. I hereby declare that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true. Further, these statements were made with the knowledge that willful false statements and the lie so made are punishable by fine, imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-identified patent.


11/29/24