IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
AT CLARKSBURG

REGENERON PHARMACEUTICALS, INC., Plaintiff, v. MYLAN PHARMACEUTICALS INC. and BIOCON BIOLOGICS INC., Defendants.	Civil Action No. 1:22-cv-00061-TSK

DEFENDANTS' OPENING POST TRIAL BRIEF – ISSUES
WHERE DEFENDANTS BEAR THE BURDEN OF PROOF

TABLE OF CONTENTS

I. INTRODUCTION. 1

II. GENERAL BACKGROUND. 2

III. CLAIM CONSTRUCTION. 2

IV. THE SCOPE, CONTENT, AND STATE OF THE ART. 2

A. Anti-VEGF targets, and the anti-VEGF aflibercept molecule. 3

B. Formulating anti-VEGF compounds. 3

C. The utility of anti-VEGF compounds. 4

1. Genentech—preclinical Lucentis (ranibizumab). 4

2. Regeneron—preclinical aflibercept. 4

3. Avastin (bevacizumab)—approved anti-VEGF cancer drug; used by physicians intravitreally to target wet AMD and DME. 5

4. Lucentis (ranibizumab) human clinical trials. 6

5. Aflibercept human clinical trials. 6

V. LEGAL STANDARDS 7

VI. THE ASSERTED DOSING CLAIMS ARE INVALID. 8

A. Claim 6 of the '572 patent is both anticipated and obvious. 9

1. The level of ordinary skill; the scope and content of the prior art. 9

2. The differences, if any, between the claims and the prior art. 9

a. Claim 6 is anticipated by Dixon (DTX 204). 10

b. Claim 6 was obvious over Dixon (DTX 204) alone or combined with Hecht (DTX 3588). 11

c. Secondary considerations do not save claim 6. 12

B. Claim 25 of the '572 patent and claims 11 and 19 of the '601 patent are anticipated and obvious. 12

1. The level of ordinary skill; the scope and content of the prior art. 12

Regeneron Pharmaceuticals, Inc. Exhibit 2018 Page 2
Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

2. The differences (if any) between the claims and the prior art. 13

a. The Regeneron Press Release (DTX 3198) anticipates claim 25 of the '572 patent and claims 11 and 19 of the '601 patent. 14

b. Any differences between claim 25 of the '572 patent and claims 11 and 19 of the '601 patent would have been obvious. 15

3. Secondary considerations do not save the claims here. 17

C. The Asserted Dosing Claims fail to comply with Section 112 requirements. 18

1. Claim 6 of the '572 patent fails to comply with Section 112. 18

2. The 5 starting dose elements lack written description and enablement. 19

a. There are no blaze marks as written description requires. 19

b. Regeneron's obviousness arguments undermine both the "blaze marks" and enablement. 19

3. The "approximately" term is indefinite. 20

VII. THE ASSERTED FORMULATION CLAIMS ARE INVALID; THEY COVER KNOWN AND OBVIOUS FORMULATIONS, AND CLAIMED TOO BROADLY. 21

A. The Asserted Formulation Claims Are Anticipated. 22

1. Dix '226 (or iterations thereof) anticipates. 22

B. The claims cover formulations that follow the Genentech Lucentis and/or Liu's established pathways, which would have been obvious to a POSA. 23

1. Level of ordinary skill; scope and content of the prior art. 23

2. The differences, if any, between the claims and the prior art. 24

a. Aflibercept (Fraser) + Lucentis formulation. 24

b. Aflibercept (Fraser) + Liu to optimize the formulation. 24

c. Dix '226, alone or in view of the knowledge of a POSA. 25

3. Secondary considerations. 26

C. The Asserted Formulation Claims Are Invalid Under Section 112. 28

1. "Suitable for intravitreal administration" is indefinite. 28

2. The written description fails to show possession of the full claim scope. 29

3. Practicing the full claim scope imposes undue burdens on the POSA. 30

VIII. CONCLUSION. 30

TABLE OF AUTHORITIES

Cases

Abbott Lab'ys v. Andrx Pharms., Inc.,
452 F.3d 1331 (Fed. Cir. 2006) 17

Abbott Lab'ys v. Sandoz, Inc.,
566 F.3d 1282 (Fed. Cir. 2009) 10

AK Steel Corp. v. Sollac & Ugine,
344 F.3d 1234 (Fed. Cir. 2003) 1

Almirall, LLC v. Amneal Pharms. LLC,
28 F.4th 265 (Fed. Cir. 2022) 26

Amgen Inc. v. Sanofi,
143 S. Ct. 1243 (2023) 1, 8, 18

Ariad Pharms., Inc. v. Eli Lilly & Co.,
598 F.3d 1336 (Fed. Cir. 2010) 8, 29

Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.,
501 F.3d 1274 (Fed. Cir. 2007) 30

Bayer Pharma AG v. Watson Lab'ys, Inc.,
874 F.3d 1316 (Fed. Cir. 2017) 12

Blue Calypso, LLC v. Groupon, Inc.,
815 F.3d 1331 (Fed. Cir. 2016) 15

Brenner v. Manson,
383 U.S. 519 (1966) 8

Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.,
752 F.3d 967 (Fed. Cir. 2014) 8

Connell v. Sears, Roebuck & Co.,
722 F.2d 1542 (Fed. Cir. 1983) 11, 25

Datamize, LLC v. Plumtree Software, Inc.,
417 F.3d 1342 (Fed. Cir. 2005) 28, 29

E.I. DuPont de Nemours & Co. v. Synvina C.V.,
904 F.3d 996 (Fed. Cir. 2018) 25, 26

Eli Lilly & Co. v. Barr Lab'ys, Inc.,
251 F.3d 955 (Fed. Cir. 2001) 15

Regeneron Pharmaceuticals, Inc. Exhibit 2018 Page 5
Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

Galderma Lab'ys, L.P. v. Tolmar, Inc.,
737 F.3d 731 (Fed. Cir. 2013) 12, 16

Genentech, Inc. v. Hospira, Inc.,
946 F.3d 1333 (Fed. Cir. 2020) 15, 16, 22

Genentech, Inc. v. Novo Nordisk A/S,
108 F.3d 1361 (Fed. Cir. 1997) 30

Guangdong Alison Hi-Tech Co. v. Int'l Trade Comm'n,
936 F.3d 1353 (Fed. Cir. 2019) 28

Hoffmann-La Roche Inc. v. Apotex Inc.,
748 F.3d 1326 (Fed. Cir. 2014) 16, 17, 26

HZNP Meds. LLC v. Actavis Lab'ys UT, Inc.,
940 F.3d 680 (Fed. Cir. 2019) 20

In re Aller,
220 F.2d 454 (C.C.P.A. 1955) 26

In re Baxter Travenol Labs,
952 F.2d 388 (Fed. Cir. 1991) 10

In re Copaxone Consol. Cases,
906 F.3d 1013 (Fed. Cir. 2018) 8, 15

In re Huai-Hung Kao,
639 F.3d 1057 (Fed. Cir. 2011) 8

In re Wands,
858 F.2d 731 (Fed. Cir. 1988) 30

Ineos USA LLC v. Berry Plastics Corp.,
783 F.3d 865 (Fed. Cir. 2015) 15, 22

Interval Licensing LLC v. AOL, Inc.,
766 F.3d 1364 (Fed. Cir. 2014) 28

Kao Corp. v. Unilever U.S., Inc.,
441 F.3d 963 (Fed. Cir. 2006) 17

KSR Int'l Co. v. Teleflex Inc.,
550 U.S. 398 (2007)..... 2, 8, 12, 16

Liebel-Flarsheim Co. v. Medrad, Inc.,
481 F.3d 1371 (Fed. Cir. 2007) 20

Regeneron Pharmaceuticals, Inc. Exhibit 2018 Page 6
Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

Merck & Co., Inc. v. Teva Pharms. USA, Inc.,
395 F.3d 1364 (Fed. Cir. 2005) 27

Microsoft Corp. v. i4i Ltd. P'ship,
564 U.S. 91 (2011)..... 7

Nautilus, Inc. v. Biosig Instruments, Inc.,
572 U.S. 898 (2014)..... 20, 28

Novo Nordisk A/S v. Caraco Pharm. Lab'ys, Ltd.,
719 F.3d 1346 (Fed. Cir. 2013) 12

PAR Pharm., Inc. v. TWI Pharms., Inc.,
773 F.3d 1186 (Fed. Cir. 2014) 12

PharmaStem Therapeutics, Inc. v. ViaCell, Inc.,
491 F.3d 1342 (Fed. Cir. 2007) 11

Purdue Pharma L.P. v. Faulding Inc.,
230 F.3d 1320 (Fed. Cir. 2000) 8, 19

Rasmusson v. SmithKline Beecham Corp.,
413 F.3d 1318 (Fed. Cir. 2005) 30

Richardson-Vicks Inc. v. Upjohn Co.,
122 F.3d 1476 (Fed. Cir. 1997) 24

Schering Corp. v. Geneva Pharms.,
339 F.3d 1373 (Fed. Cir. 2003) 8

Scripps Clinic & Rsch. Found. v. Genentech, Inc.,
927 F.2d 1565 (Fed. Cir. 1991) 10

Senju Pharm. Co. v. Lupin Ltd.,
780 F.3d 1337 (Fed. Cir. 2015) 24

UCB, Inc. v. Actavis Lab'ys UT, Inc.,
65 F.4th 679 (Fed. Cir. 2023) 26

Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC,
683 F.3d 1356 (Fed. Cir. 2012) 14

Statutes

35 U.S.C. § 102..... 1, 2, 8

35 U.S.C. § 102(b) 24

35 U.S.C. § 102(e) 25

Regeneron Pharmaceuticals, Inc. Exhibit 2018 Page 7
Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

35 U.S.C. § 103 ..... 1, 2, 8

35 U.S.C. § 103(c) 25

35 U.S.C. § 112 ..... passim

TABLE OF ABREVIATIONS

Abbreviation	Description
'572 patent	U.S. Patent No. 11,253,572 B2 (PTX 3)
'601 patent	U.S. Patent No. 10,888,601 B2 (PTX 1)
'747 patent	U.S. Patent No. 7,303,474 B2 (DTX 2730)
'865 patent	U.S. Patent No. 11,084,865 B2 (PTX 2)
'959 patent	U.S. Patent No. 7,070,959 B1 (DTX 7)
µL	Microliter
AIA	Leahy-Smith America Invents Act
AMD	Age-related macular degeneration
ARVO	Association for Research in Vision and Ophthalmology
ASRS	American Society of Retinal Specialists
Asserted Claims	Claims 11 and 19 of the '601 patent, claims 6 and 25 of the '572 patent, and claims 4, 7, 9, 11, and 14-17 of the '865 patent
Asserted Dosing Claims	Claims 11 and 19 of the '601 patent and claims 6 and 25 of the '572 patent
Asserted Formulation Claims	Claims 4, 7, 9, 11, and 14-17 of the '865 patent
Asserted Patents	U.S. Patent No. 10,888,601 B2 (PTX 1), U.S. Patent No. 11,084,865 B2 (PTX 2), and U.S. Patent No. 11,253,572 B2 (PTX 3)
Avery	Robert L. Avery et al., *Intravitreal Bevacizumab (Avastin) for Neovascular Age-Related Macular Degeneration*, 113 OPHTHALMOLOGY 363 (2006) (DTX 9036)
Bashshur	Ziad F. Bashshur et al., *Intravitreal Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration: A One-year Prospective Study*, 145 AMERICAN J. OPHTHALMOLOGY 249 (2008) (DTX 4013)
BCVA	Best corrected visual acuity
Chang	Byeong S. Chang & Susan Hershenson, *Practical Approaches to Protein Formulation Development*, *in* RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS, 1 (John F. Carpenter & Mark C. Manning eds., 2002) (PTX 1832)

Abbreviation	Description
CLEAR-IT 1	Regeneron, Phase I Study, Aflibercept in AMD, An Exploratory Study of the Safety, Tolerability and Biological Effect of Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration
CLEAR-IT 2	Regeneron, Phase II Study, Aflibercept in AMD, A Randomized, Controlled Study of the Safety, Tolerability and Biological Effect of Repeated Intravitreal Administration of VEGF Trap in Patients With Neovascular Age-Related Macular Degeneration
CRVO	Central retinal vein occlusion
Defendants	Biocon Biologics Inc. and Mylan Pharmaceuticals Inc.
Defs.' FOF	Defendants' Proposed Findings of Fact and Conclusions of Law
Dix '226	U.S. Patent No. 10,406,226 B2 (DTX 13)
Dixon	James A. Dixon et al., *VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration*, 18 EXPERT OPINION INVESTIGATIONAL DRUGS 1573 (2009) (DTX 204)
DME	Diabetic macular edema
Do 2009	D.V. Do et al., *An Exploratory Study of the Safety, Tolerability and Bioactivity of a Single Intravitreal Injection of Vascular Endothelial Growth Factor Trap-Eye in Patients with Diabetic Macular Oedema*, 93 J. OPHTHALMOLOGY 144 (2009) (DTX 3102)
DR	Diabetic retinopathy
FDA	United States Food and Drug Administration
Fraser	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 CLINICAL ENDOCRINOLOGY & METABOLISM 1114 (2005) (DTX 729)
Gaudreault	Jacques Gaudreault et al., *Preclinical Pharmacokinetics of Ranibizumab (rhuFabV2) after a Single Intravitreal Administration*, 46 INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE 726 (2005) (DTX 2265/PTX 1839)
Hecht	Gerald Hecht, *Ophthalmic Preparations*, *in* 2 REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 1563 (Alfonso R. Gennaro et al. eds.,19th ed. 1995) (DTX 3588)

Abbreviation	Description
Holash	Jocelyn Holash et al., *VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects*, 99 PNAS 11393 (2002) (DTX 3549)
Lalwani	Geeta A. Lalwani, *Anti-VEGF Therapy in Diabetic Macular Edema*, RETINA TODAY 45 (Sept. 2009) (DTX 2733)
Liu	US. Patent Application Publication No. 2004/0197324 A1 (DTX 730)
mg	Milligram
mL	Milliliter
PANORAMA	Regeneron, Phase III Study, Aflibercept in DR, A Phase 3, Double-Masked, Randomized Study of the Efficacy and Safety of Intravitreal Aflibercept Injection in Patients With Moderately Severe to Severe Nonproliferative Diabetic Retinopathy
PBS	Phosphate buffered saline
Peyman	International Patent Publication No. WO 2005/102303 A2 (PTX 1758)
POSA	Person of ordinary skill in the art
PRN	*Pro re nata* or as-needed dosing
PrONTO	Genentech, Phase II Study, Ranibizumab in AMD, Prospective Optical Coherence Tomography (OCT) Imaging of Patients With Neovascular Age-Related Macular Degeneration (AMD) Treated With Intra-Ocular Lucentis™ (Ranibizumab): PrONTO Study
PTAB	Patent Trial and Appeal Board
PTO	United States Patent and Trademark Office
PVR	Proliferative vitreoretinopathy
Regeneron	Regeneron Pharmaceuticals, Inc.
Regeneron Press Release	Regeneron Press Release, Enrollment Completed in Regeneron and Bayer HealthCare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD) (September 14, 2009) (DTX 3198)
RVO	Retinal vein occlusion
Tr.	Trial Transcript
VEGF	Vascular endothelial growth factor
VEGF Trap	Regeneron development name for aflibercept

Abbreviation	Description
VISTA	Regeneron, Phase III Study, Aflibercept in DME, A Double-Masked, Randomized, Active-Controlled, Phase 3 Study of the Efficacy and Safety of Intravitreal Administration of VEGF Trap-Eye in Patients With Diabetic Macular Edema
VIVID	Regeneron, Phase III Study, Aflibercept in DME, A Randomized, Double Masked, Active Controlled, Phase III Study of the Efficacy and Safety of Repeated Doses of Intravitreal VEGF Trap-Eye in Subjects With Diabetic Macular Edema

TABLE OF RECORD CITATIONS

Abbreviation	Description
Dkt. 427	Order on Claim Construction (April 19, 2023)
Dkt. 494-9	Joint Pretrial Order Memorandum, Exhibit 5P, Plaintiff's Brief Summary of Material Facts and Theories of Liability or Defense (May 26, 2023)
Dkt. 494-12	Joint Pretrial Order Memorandum, Exhibit 7, Stipulated Facts (May 26, 2023)
Dkt. 553	Joint Stipulation Regarding Commercial Success (June 22, 2023)

I. INTRODUCTION.

A patent's "term of 'protection from competitive exploitation'" is limited. *Amgen Inc. v. Sanofi*, 143 S. Ct. 1243, 1251 (2023). Regeneron had a huge family of patents that covered the aflibercept molecule and its anti-VEGF use. On June 16, 2023, the last of those patents officially expired,[1] placing aflibercept in the public domain—the final exchange in the *quid pro quo* that Regeneron agreed to for U.S. patent protection over its molecule. The Asserted Claims here will renege on that bargain, because they cover aflibercept in dosing regimens that *also* were in the public domain (claims 6 and 25 of the '572 patent, claims 11 and 19 of the '601 patent); and putting aflibercept in known formulations (one that is "isotonic" for the '572 patent claim 6; the one for Lucentis, or the one for high concentrations that are stable in Liu, for the '865 patent claims).

The Asserted Claims also cover steps to achieve known and routine goals, such as administering monthly starting doses sufficient to dry the macula (the claimed number of 5 falls within that range), before moving to extended 8-week dosing intervals; making a formulation isotonic (to be comfortable and non-irritating to the eye as in Dixon); ensuring a stable formulation (which Lucentis was, and which was Liu's stated goal); measuring native conformation using size exclusion chromatography; and optimizing concentrations (the industry standard).

Work building on a prior invention, to be patentable, must be novel, non-obvious, and give the public a new *quid pro quo* benefit. *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003); 35 U.S.C. §§ 102, 103, 112. The claims cover what was old and obvious; and the specifications don't solve the issues that Regeneron's witnesses argued made what is claimed non-routine (*e.g.*, show that more monthly doses or formulations with high concentrations work in humans). (Tr. 498:2-16, 499:8-11 (Furfine); Tr. 2155:11-13, 2155:21-2156:11, 2167:13-2168:21,

[1] DTX 3501.12 ('959 PTE); DTX 7 ('959 patent), among others; Tr. 1432:8-1438:24 (MacMichael).

2176:18-20 (Trout); Tr. 1927:6-25, 1933:21-25 (Csaky)). The Asserted Claims are invalid.

II. GENERAL BACKGROUND.

Patents are assessed from the perspective of a POSA. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007). The parties' few POSA differences do not alter the ultimate outcome of those analyses. (Tr. 1372:15-1374:4 (MacMichael); Tr. 1008:25-1012:13 (Rabinow); Tr. 752:5-753:21, 755:22-756:6 (Albini); Tr. 1270:19-1271:11 (Stewart); Tr. 2011:5-2012:6 (Trout); Tr. 1815:20-1816:3 (Csaky)).

Aflibercept was a known, potent, VEGF blocker. (Tr. 114:16-17 (Yancopoulos); DTX 3549 (Holash)). But it was Genentech's prior anti-VEGF work with bevacizumab (Avastin) in 2003, and ranibizumab (Lucentis) in 2005, that were the "game changers" that blazed a trail that aflibercept followed. (Tr. 185:23-186:15 (Yancopoulos)). Once FDA approved Avastin in 2003, and Genentech reported ranibizumab human clinical data in 2005, physicians injected intravenous bevacizumab to treat AMD and DME *without* a specific intravitreal formulation, and *without* Phase III clinical safety and efficacy data. (Tr. 764:5-17 (Albini); Tr. 1030:13-1031:2 (Rabinow); DTX 3058 (Rosenfeld); DTX 9036 (Avery); DTX 4041 (Ferrara 2005)). The dosing and formulation art rapidly advanced without regard to Regeneron's patents. (*See, e.g.*, Tr. 515:19-25 (Furfine); Tr. 2138:2-24 (Trout); DTX 3058; DTX 9036; DTX 2265 (Gaudreault); DTX 726 (Shams)).

III. CLAIM CONSTRUCTION.

The Court has correctly construed the claims. (Dkt. 427). The parties presented their cases at trial in reliance thereon. (*See, e.g.*, Tr. 16, 18-19, 40, 59, 72 (opening statements), 316, 353-54, 588, 591, 600, 602, 615, 626, 630, 649, 696-97, 810-11, 813, 829, 1008 (experts' opinions)).

IV. THE SCOPE, CONTENT, AND STATE OF THE ART.

Pre-AIA 35 U.S.C. §§ 102 and 103 apply here. Detailed legal standards; what prior art and conception contentions were timely raised; and the references that are prior art across Regeneron's

multiple proposed invention dates shall be set forth in Defs.' FOF. Defendants mainly focus on art stipulated as prior art to the Asserted Patents. (Dkt. 494-12).

A. Anti-VEGF targets, and the anti-VEGF aflibercept molecule.

By 2005, the literature confirmed that "[i]nhibiting angiogenesis" was "a promising strategy" to treat cancer and "age-related macular degeneration," with "the first antiangiogenic agents … recently approved for use in several countries." (DTX 4041.1). Regeneron's prior art patents and publications also tout anti-VEGFs as "useful" to treat "VEGF-induced pathological angiogenesis" and "eye disorders such as age related macular degeneration and diabetic retinopathy." (DTX 3619.6, ll. 8-13; *see also* DTX 3619.36-37). VEGF was a known target.

Regeneron tried to argue a POSA didn't know aflibercept's exact structure. Regeneron disclosed $VEGF_{R1R2}Fc\Delta Cl(a)$, its full sequence, and better properties before 2006. (*See* DTX 3619.60; DTX 3619.139-141; DTX 7.1; DTX 7.42-44; DTX 7.63, 9:65-67; DTX 7.73, 29:13:29; Tr. 1432:19-1433:23 (MacMichael)). A POSA thus knew aflibercept's structure and sequence, whatever the name. (DTX 3549; DTX 3619; DTX 4008; DTX 7; DTX 728; Tr. 1227:9-12 (Chu 30(b)(6)); Tr. 110:11-22 (Yancopoulos); Tr. 762:2-8 (Albini); Tr. 1014:18-1015:8 (Rabinow)).

B. Formulating anti-VEGF compounds.

Regeneron's early aflibercept injection formulations used an aqueous PBS vehicle that the art called isotonic. (DTX 3549.2; DTX 8180 (calling it isotonic)). Regeneron's animal studies had recipes for high aflibercept concentrations, in a formulation with the classic buffer, surfactant, and stabilizer ingredients. (DTX 728.2; DTX 718.1). Fraser's animal studies also used a high concentration aflibercept formulation, also with a buffer, surfactant, and stabilizer, using "buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20 [surfactant], with either 20% glycerol or 20% sucrose [stabilizer]." (DTX 729.2).

Regeneron filed patents to more stable anti-VEGF formulations, such as Dix '226 (DTX

13.4, 1:39 ("pharmaceutical formulations having increased stability.")). Stable formulation Examples used high concentration aflibercept, phosphate buffer, polysorbate, and sucrose as a stabilizer; the specification also discussed formulations with a "a buffer, a co-solvent, and one or more stabilizers," a "preferred" range of 10-50 mg/mL; and a "40 mg/mL" embodiment. (DTX 13.5, 3:60-61; 13.7, 7:1-10, 7:60-8:40). The original application and publication also had, among others, 40 mg/mL liquid aflibercept with a buffer, polysorbate 20, and stabilizer. (DTX 4121.1, 3 [0017], 5 [0036]; Tr. 1788:8-13, 1789:18-1790:1, 1790:14-17 (Graham)).

The art also included ranibizumab formulations (including a clinical trial formulation stable and suitable for human intravitreal use), also with the classic buffer, surfactant, and stabilizer. (DTX 2265; DTX 726; Tr. 1034:21-1037:21, 1042:9-1044:9, 1045:9-14 (Rabinow)).

C. The utility of anti-VEGF compounds.

By 2005, clinicians used anti-VEGF strategies to treat their patients, including with intravitreal injections, for the clinical indications of AMD, DME, and DR.

1. Genentech—preclinical Lucentis (ranibizumab).

Regeneron monitored how Genentech dosed ranibizumab for eye diseases, and by March 1, 2004, knew that Genentech had reported that the "highest levels [of ranibizumab were] observed for ITV," intravitreal doses. (*See, e.g.*, DTX 710.1-2; DTX 2265.1 (Genentech comparing how ranibizumab performed intravitreally and intravenously in monkeys, and reporting ranibizumab would be "favorable for its clinical use in treating neovascular AMD by monthly ITV injection."); Tr. 247:16-248:12 (Furfine); Tr. 1605:19-22 (Graham)). In February 2005, Gaudreault published a primate study comparing intravitreal and intravenous ranibizumab formulations, including 10 mg/mL and 40 mg/mL in 50 µLs dosed intravitreally. (DTX 2265.2).

2. Regeneron—preclinical aflibercept.

By 2002, Regeneron published that the "combination of high-affinity and improved

pharmacokinetics" made "VEGF-Trap$_{R1R2}$ one of the most, if not the most, potent and efficacious VEGF blocker available." (DTX 3549.5; Tr. 1252:4-14 (Chu)). In 2003, Regeneron published studies on aflibercept injected into mice eyes. (DTX 2751.1; Tr. 1050:21-1052:3, 1090:5-1092:3 (Rabinow)). One intravitreal injection of VEGF-Trap$_{R1R2}$ "markedly suppressed the development of choroidal neovascularization." (DTX 2751.7). In 2005, Regeneron published Fraser, a dose-ranging study to find "the minimal dose of VEGF Trap$_{RIR2}$" producing the anti-VEGF effect. (DTX 729.2). VEGF Trap$_{R1R2}$ "was well tolerated." (DTX 729.3). The 4 mg/kg and the 1 mg/kg doses "resulted in a significantly longer" period of activity. (DTX 729.5).

Regeneron also praised aflibercept's performance in animal studies for showing "impressive efficacy in an assortment of animal models of these eye diseases," including diabetic edema, retinopathy, and AMD. (DTX 3592.4; *see also* DTX 2730 (Regeneron '747 patent emphasizing efficacy of VEGF$_{R1R2}$FcΔCl(a), collecting animal testing data, and discussing treating AMD with intravitreal injections of aflibercept in human patients); DTX 4229.24 [0031] (published patent application reporting results of intravitreal aflibercept injections)).

3. Avastin (bevacizumab)—approved anti-VEGF cancer drug; used by physicians intravitreally to target wet AMD and DME.

FDA approved the anti-VEGF Avastin (bevacizumab) as an intravenous anti-cancer therapy in 2004. (DTX 210.2; DTX 3510). By March 2005, physicians reported successfully using Avastin intravitreally to treat wet AMD. (DTX 210; Tr. 1240:22-1242:19 (Chu 30(b)(6))). The study lead, Dr. Phil Rosenfeld, explained that "[w]e've been injecting anti-VEGF drugs into the eye for the past 3 years with very encouraging results." (DTX 210.1). Details about dosing this intravenous formulation in humans, intravitreally, was also published. (*See* DTX 3058.2; Tr. 528:2-12 (Furfine); DTX 9036.5-6 (dosing 1.25 mg of Avastin in 0.05 mL)).

Physicians also used Avastin in clinical trials with extended dosing intervals, with

Bashshur reporting in 2008 that after three monthly injections, visual acuity gains could be maintained for several months by giving just 3.4 injections on average for the remainder of the year. (DTX 4013.3; *see also* Tr. 768:2-10 (Albini) (summarizing DTX 4013)).

4. Lucentis (ranibizumab) human clinical trials.

At the July 2005 ASRS meeting, the results from a "large phase III clinical trial" (PrONTO) demonstrated that ranibizumab was "effective in the treatment of neovascular AMD." (DTX 9036.5-6; *see also id.* at 13). Dr. Rosenfeld presented further one-year PrONTO outcomes at the May 2006 ARVO meeting. (*See* DTX 218.2). Dr. Shams' patent application published in May 2006 with a study protocol for the "efficacy and safety of intravitreal injections of VEGF antagonist (e.g., ranibizumab) administered monthly for 3 doses followed by doses every 3 months." (DTX 726.32). Shams' publication also provided a detailed formulation. (*Id.*) FDA approved Lucentis for wet AMD in June 2006. (DTX 3040.1).

Once ranibizumab's efficacy for AMD was established, physicians used it for other indications, namely DME, DR, and RVO, and also on extended dosing intervals. Lalwani discussed dosing DME patients with three monthly doses of ranibizumab (baseline, month 1, month 2), followed by dosing at an extended two-month interval, at months 4 and 6, for a mean gain of 8 letters by month 12. (DTX 2733.1; Tr. 768:24-769:14 (Albini)).

5. Aflibercept human clinical trials.

The first aflibercept Phase I study with intravenous (systemic) aflibercept was done by 2004. (DTX 207.1-2). In March 2005, Regeneron said that it would not "pursue further clinical development using systemic delivery of VEGF Trap for eye diseases," but instead "plan[ned] to initiate a clinical trial of the VEGF Trap delivered through intravitreal injection in mid-2005." (DTX 4956.4; DTX 4956.119 (March 11, 2005 date)). By late 2005, Regeneron confirmed that its "[i]nitial clinical studies in human patients suffering from both AMD and diabetic edema and

retinopathy appear quite promising," and that "VEGF Trap is now entering more advanced clinical trials in vascular eye diseases." (DTX 3592.4-5). "In February 2006, [Regeneron] announced positive preliminary results from an ongoing phase 1 dose-escalation study of the VEGF Trap-Eye." (DTX 4957.5). Regeneron presented the study results, called CLEAR-IT 1, at ARVO in May of 2006. (Tr. 1647:11-1648:22 (Chu); DTX 9006.12 (reference 56)). Intravitreal doses "of up to 4 mg of VEGF Trap" were "well-tolerated." (DTX 216.3; Tr. 1650:7-25 (Chu)). This well-tolerated dose was 8 times greater than the FDA-approved ranibizumab 0.5 mg dose.

By May 2007, Regeneron released the CLEAR-IT 2 Phase II study data for intravitreal aflibercept. (*See* DTX 232; DTX 234 (Regeneron email re ARVO posters, including CLEAR-IT 2); Tr. 1264:4-1265:16 (Chu 30(b)(6)) (confirming data was presented and public)). Regeneron published its Phase I DME data for intravitreal aflibercept, stating the 4 mg dose also was "well tolerated," had "no serious drug-related adverse events," and that just a single injection produced mean BCVA improvements of 2.6 to 6.8 letters by 6 weeks. (DTX 234.3).

Regeneron then submitted to FDA its Phase III clinical trial plan for 3 monthly doses, followed by every-8-week dosing. FDA posted the Phase III study to clinicaltrials.gov on July 31, 2007. (DTX 231.8; Tr. 1263:18-23 (Chu 30(b)(6))). In 2009, Dixon publicly disclosed that Regeneron's Phase III clinical trials included an arm with 3 doses given every 4 weeks apart, followed by dosing every 8 weeks. (DTX 204.4). Regeneron announced that its Phase III clinical trials met their primary endpoint on November 22, 2010. (DTX 917.1).

V. LEGAL STANDARDS

Facts supporting invalidity defenses must be established by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 97 (2011). When the PTO Examiner did not specifically consider art (as here), the burden of persuasion is more easily carried. *Id.* at 111.

A reference anticipates when it expressly or inherently discloses what is claimed. *Schering*

Corp. v. Geneva Pharms., 339 F.3d 1373, 1377 (Fed. Cir. 2003); 35 U.S.C. § 102. Whether claimed subject matter was obvious to a POSA under 35 U.S.C. § 103 depends on "the scope and content of the prior art; the differences between the claims and the prior art; the level of ordinary skill in the pertinent art; and any secondary considerations of non-obviousness." *In re Copaxone Consol. Cases*, 906 F.3d 1013, 1024 (Fed. Cir. 2018). Objective indicia "must always when present be considered,"[2] but "they do not necessarily control the obviousness determination." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). The analysis should not be conducted in "a narrow, rigid manner," but consider whether the claims cover "the results of ordinary innovation," which is not patentable. *KSR*, 550 U.S. at 427-28.

35 U.S.C. § 112 ensures that a patent "is not a hunting license" or a "reward for the search," but "compensation for its successful conclusion." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1353 (Fed. Cir. 2010) (en banc) (quoting *Brenner v. Manson*, 383 U.S. 519, 533 (1966)). A "patent's specification must enable a person skilled in the art to make and use" the "full scope of the invention as defined by its claims." *Amgen*, 143 S. Ct. at 1254. A specification that is a mere "'wish' or 'plan' for obtaining" the full scope of what was claimed is understood by a POSA to show that the inventors did not possess the entire scope of the claimed invention. *Ariad*, 598 F.3d at 1350. Section 112 compliance is measured as of the patent's filing date. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326-27 (Fed. Cir. 2000).

VI. THE ASSERTED DOSING CLAIMS ARE INVALID.

Claim 6 of the '572 patent claims treating angiogenic eye disorders by intravitreally dosing 2 mg of aflibercept in an isotonic solution using a particular dosing regimen. Claim 25 of the '572

[2] Regeneron has the initial production burden for secondary considerations evidence, and show "a nexus" to "the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

patent and claim 11 of the '601 patent are directed to treating DME every 4 weeks for the first 5 injections followed by an 8-week dosing interval. Claim 19 of the '601 patent uses this regimen for DR. (*See* Tr. 756:22-757:3, 780:5-10, 787:1-17, 811:9-12 (Albini); Tr. 1271:16-19, 1272:9-15 (Stewart); Tr. 1865:25-1866:6 (Csaky)). Regeneron argues the "isotonic" and the 5 injections part of the regimen differentiate the claims from the prior art. They do not, because they were known and obvious. Nor do these claims comply with 35 U.S.C. § 112.

A. Claim 6 of the '572 patent is both anticipated and obvious.

Claim 6 is anticipated if the formulations Dixon (DTX 204) identified were inherently isotonic.[3] Claim 6 is also obvious if a POSA viewing Dixon had a reason to use an isotonic formulation with a reasonable expectation of success in making an isotonic aflibercept dose.

1. The level of ordinary skill; the scope and content of the prior art.

As noted in Section II, above, the parties largely agree on the POSA skill set. Regeneron did not dispute that the prior art's scope and content includes Dixon (DTX 204), published in 2009, and Hecht (DTX 3588), published in 1995. (Dkt. 494-12).

2. The differences, if any, between the claims and the prior art.

Claim 1, incorporated into claim 6, covers Dixon's disclosure of a 2 mg aflibercept intravitreal dose, given in a regimen of 3 monthly doses, followed by an 8-week interval. (DTX 204.4; Tr. 769:18-770:3, 811:19-813:3 (Albini); Tr. 1926:10-1927:5 (Csaky)). Dixon also taught that aflibercept is "formulated with different buffers and at different concentrations (for buffers in common) suitable for the comfortable, non-irritating, direct injection into the eye." (DTX 204.3; Tr. 826:19-23 (Albini); Tr. 1098:23-1099:4 (Rabinow)).

[3] Anticipation based on the '747 patent (DTX 2730), will be set forth in more detail in Defs.' FOF.

a. Claim 6 is anticipated by Dixon (DTX 204).

Dixon "referred to" Regeneron's Phase III 2 mg dose used in the claimed dosing regimen; and that dose actually "utilized" the Eylea® formulation. *See In re Baxter Travenol Labs*, 952 F.2d 388, 390 (Fed. Cir. 1991). Extrinsic evidence may be considered to explain, but not expand, the meaning of a reference. *Scripps Clinic & Rsch. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576-77 (Fed. Cir. 1991), *overruled on other grounds by Abbott Lab'ys v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009). The Phase III clinical trials actually used the Eylea® formulation. (Tr. 214:18-24 (Yancopoulos); DTX 5073.9). "That fact, coupled with" Dr. Trout's testimony that an iso-osmotic formulation is isotonic,[4] "leads to the unmistakable conclusion that the claims at issue were anticipated." *Baxter*, 952 F.2d at 390.

Independently, a POSA understood that Dixon's description of the aflibercept eye formulation as having "buffers" to be "suitable for the comfortable, non-irritating, direct injection into the eye" (DTX 204.3) means the formulation is inherently isotonic. (Tr. 1098:23-1099:22 (Rabinow); Tr. 828:16-19 (Albini)). Dr. Trout did not dispute inherency. (Tr. 2117:21-24 (Trout) (only obviousness opinions)). Thus, Regeneron's only defense is that Dr. Rabinow's inherency opinion "did not hold up" at deposition, because he did not know whether a particular ***hypertonic*** solution was comfortable or non-irritating. (Tr. 816:4-5 (emphasis added); *see also id*. 39:7-9 (Regeneron Opening Statement)). For "comfortable" and "non-irritating" to not mean all isotonic formulations, Regeneron needed to find an isotonic aflibercept formulation that ***was not*** comfortable, and that ***did*** irritate the eye. It identified none at trial. Dr. Rabinow reiterated his opinion that a POSA understood that the comfortable and non-irritating aflibercept formulations

[4] For infringement, Dr. Trout insisted that the YESAFILI™ formulation was isotonic because the labeling stated the formulation was iso-osmotic, which "is synonymous with isotonic." (Tr. 640:20-25, 642:5-22 (Trout)). The FDA-approved Eylea® labeling likewise calls the Eylea® formulation iso-osmotic. (DTX 3316.9; *see also* DTX 9038.2; Tr. 641:6-10, 642:2-4 (Trout)).

discussed in Dixon are isotonic. (Tr. 1098:23-1099:22 (Rabinow); *see also* Tr. 913:21-914:6 (Albini)). Dixon anticipates.

b. Claim 6 was obvious over Dixon (DTX 204) alone or combined with Hecht (DTX 3588).

Since Dixon anticipates claim 6, claim 6 is also obvious, for "anticipation is the epitome of obviousness." *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983).

As noted above, Dixon discusses aflibercept formulations. (DTX 204.3; Tr. 826:19-23 (Albini); Tr. 1098:23-1099:4 (Rabinow)). A POSA needing more formulation information would turn to Remington's Pharmaceutical Sciences. (PTX 1.13, 5:55-59; PTX 3.16, 5:64-6:1 (Remington's is "known to all pharmaceutical chemists"); Tr. 2093:14-16 (Trout) ("Remington's is a general textbook" of "different chapters, formulation and others, by experts")).

Hecht is the Remington's chapter specifically directed to ophthalmic formulations. (DTX 3588.1-5). Hecht taught that "[o]phthalmic solutions are formulated to be sterile, isotonic, and buffered for stability and comfort," and that "[g]iven a choice, isotonicity always is desirable and particularly is important in intraocular solutions." (DTX 3588.11, 13). That is more than enough to render the use of an isotonic formulation obvious for intravitreal dosing.

There also are only three tonicity options to try for a formulation: isotonic, hypertonic, or hypotonic. (Tr. 212:21-24 (Yancopoulos)). The specifications of the '572 and '601 patents admit that useful formulations for the claimed methods were those "conventionally used for injections," including isotonic solutions. (PTX 1.13, 6:8-20; PTX 3.13, 6:18-30). "Admissions in the specification regarding the prior art are binding on the patentee" for "obviousness." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007). All claim 6 does then is "simply arrange[] old elements" of the known Phase III regimen in Dixon and a known isotonic formulation; the latter performs "the same function it had been known to perform," including in

Dixon (comfortable and non-irritating), rendering the combination obvious. *KSR*, 550 U.S. at 417; *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737-38 (Fed. Cir. 2013); *Novo Nordisk A/S v. Caraco Pharm. Lab'ys, Ltd.*, 719 F.3d 1346, 1353-56 (Fed. Cir. 2013).

Dr. Rabinow reiterated that a POSA was motivated to develop an isotonic formulation. (Tr. 1173:25-1174:4). Regeneron responded that a hypertonic formulation existed. (Tr. 212:14-24 (Yancopoulos) (proposing hypertonic solutions could be "[o]pthalmically compatible")). Even assuming that is true, the law does not require the prior art to motivate towards the *best* option, only a *suitable* one. *Bayer Pharma AG v. Watson Lab'ys, Inc.*, 874 F.3d 1316, 1328 (Fed. Cir. 2017) (citing *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1197-98 (Fed. Cir. 2014)). Hecht noted that "isotonicity always is desirable," clearly teaching its suitability. (DTX 3588.13).

c. Secondary considerations do not save claim 6.

Regeneron did not proffer any secondary considerations associated with the "isotonic" claim element, let alone within the claimed regimen. (Tr. 2083:8-2088:10 (Trout) (assigning Eylea® success to the '865 patent); Tr. 1914:9-1919:11 (Csaky) (assigning long-felt need, failure of others, praise, etc. to regimens that reduced the number of office visits)).

* * *

Thus, viewing the art as a whole, the claimed isotonic formulation would have been both obvious, and obvious to try, rendering claim 6 invalid for obviousness.

B. Claim 25 of the '572 patent and claims 11 and 19 of the '601 patent are anticipated and obvious.

A POSA could envision the use of 5 doses spaced 4 weeks apart before using an 8-week dose; and a POSA had a "good reason to pursue" this option. *KSR*, 550 U.S. at 402.

1. The level of ordinary skill; the scope and content of the prior art.

As noted in Section II, above, the parties largely agree on the POSA skill set. Regeneron stipulated the Regeneron Press Release (DTX 3198), describing the DME PRN dosing regimen

following three required monthly loading doses; Do 2009 (DTX 3102), which dosed aflibercept in DME patients; and Lalwani (DTX 2733), discussing ranibizumab use for DME, were prior art. (Dkt. 494-12).

2. The differences (if any) between the claims and the prior art.

Physicians had long dosed anti-VEGF compounds in extended dosing regimens preceded by monthly/4 week doses. The art discussed treating AMD "with ranibizumab monthly until optical coherence tomography (OCT) shows the macula to be completely free of fluid. Some patients reach that point after 2 injections; others require as many as 8 injections. When the macula is dry, I withhold treatment and bring the patient back in 2 months." (DTX 2035.1).

Dr. Csaky argued that DME was a "completely different disease" compared to AMD. (Tr. 1838:9-16 (Csaky)). But Lalwani reiterated that "investigations of novel therapies to treat neovascular age-related macular degeneration (AMD) have spilled over into the treatment of diabetic macular edema (DME)," because "VEGF has been shown to play a crucial role in the pathogenesis of DME." (DTX 2733.1). Lalwani noted that the READ 1 study tested ranibizumab for DME "at baseline, month 1, 2, 4 and 6 months," leading to a gain in visual acuity. (*Id.*; Tr. 792:3-12 (Albini)). A POSA knew and expected extended-interval regimens to work for DME.

Regeneron confirmed in a September 14, 2009 Press Release that its Phase 3 CRVO study would use "six monthly intravitreal injections" of aflibercept, then dose on a "PRN (as needed) basis for another six months." (DTX 3198.2). It also disclosed its Phase II DME clinical trial with one arm dosing 2 mg every 8 weeks after three monthly loading doses; and one arm dosing "2 mg on an as-needed (PRN) basis after three monthly loading doses." (*Id.*)

The prior art thus disclosed a range of initial doses spaced 4 weeks/1 month apart, followed by extended dosing intervals, such as 8 weeks/2 months. (*See* Tr. 780:24-782:7 (Albini)).

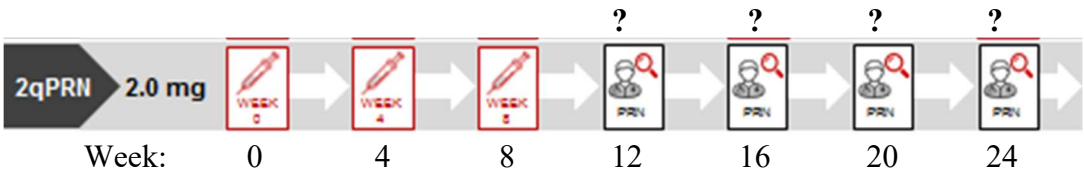
a. The Regeneron Press Release (DTX 3198) anticipates claim 25 of the '572 patent and claims 11 and 19 of the '601 patent.

The claims cover treating DME (PTX 3.25, (claim 25); PTX 1.21 (claim 11)), or DR (PTX 1.22 (claim 19)) with 2 mg aflibercept in a regimen with 5 doses spaced 4 weeks/1 month apart, followed by an 8-week dose. (*See* Tr. 756:22-757:2 (Albini); Tr. 312:13-19 (Csaky)).

Dr. Csaky conceded that the PRN DME regimen included at least 3 required monthly loading doses at weeks 0, 4 and 8, followed by PRN dosing. (Tr. 1959:2-11 (Csaky)). Dr. Albini explained that a POSA would easily envision the rest of the regimen to include one option with 5 doses, separated by 4 weeks, followed by an 8-week dose interval. (Tr. 781:19-782:7 (Albini)).

Regeneron proposed various arguments why the art did not *specifically* say 5 doses. (Tr. 1839:10-14, 1843:3-10, 1863:24-1865:2 (Csaky)). But when the prior art contemplates variability, as PRN regimens do, the "question for purposes of anticipation is" whether "the number of categories and components" in the PRN regimen "was so large that the combination of" 5 doses spaced 4 weeks apart followed by an 8 week dose "would not be immediately apparent to one of ordinary skill." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012). On this issue, Dr. Csaky was silent. That is because a POSA knew how to implement the PRN regimen to the 6-month mark after 3 doses were given 4 weeks apart; and can readily envision that the claimed 5-dose regimen is one of the existing dosing options. (Tr. 782:11-784:1 (Albini)).

Dr. Csaky admitted a POSA understood the PRN regimen included a "conditional injection," namely "question mark, does that person need an injection?" (Tr. 1960:25-1961:12 (Csaky)). That means limited options for his "question mark" scenario—to dose, or not dose:



(PDX 1.124). Dr. Csaky admitted that under the PRN regimen a patient could be dosed at weeks 12, 16 and 24, but not 20, resulting in the following dosing schedule:

Week: 0 4 8 12 16 20 24

(Tr. 1959:12-1961:24 (Csaky); PDX 1.124 (modified); DDX 13.4). This regimen represents 5 doses given every 4 weeks, followed by an 8-week dosing interval, as claim 25 of the '572 patent and claims 11 and 19 of the '601 patent require. (Tr. 782:11-784:13 (Albini); DDX 6.54-55).

Thus, the Regeneron Press Release "explicitly contemplates the combination of the disclosed functionalities" that a POSA "would be able to implement." *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1343-44 (Fed. Cir. 2016). And, since Regeneron contends that DME is a subset of DR (Tr. 1858:5-9 (Csaky); *see* Tr. 155:7-13 (Yancopoulos); Tr. 1627:3-1628:16 (Chu)), the "genus claim" 19 "is anticipated by, and therefore not patentably distinct from, an earlier species," the DME regimen. *Eli Lilly & Co. v. Barr Lab'ys, Inc.*, 251 F.3d 955, 971 (Fed. Cir. 2001).

Nor is the claimed range "critical to the operability of the claimed invention." *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1338 (Fed. Cir. 2020) (quoting *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 871 (Fed. Cir. 2015)). The Phase II DME clinical trial regimen, with three 4-week doses followed by 8-week dosing, also worked. (Tr. 202:10-203:4 (Yancopoulos) (describing the study); Tr. 247:11-249:2; *see also* Tr. 193:6-19).

Thus, claim 25 of the '572 patent and claims 11 and 19 of the '601 patent are anticipated.

b. Any differences between claim 25 of the '572 patent and claims 11 and 19 of the '601 patent would have been obvious.

A POSA, "knew that [monthly] injections were difficult to tolerate." *Copaxone*, 906 F.3d at 1021. There was an established "need to solve the problem" of patients wanting fewer injections

"by looking to less-frequent dosing regimens" than monthly. *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1332 (Fed. Cir. 2014).

Physicians had already proposed solutions known in the art: treat aggressively, early, with monthly/4-week doses until the macula is dry; then extend dosing to 2 month intervals. (DTX 2035.2). By 2010, over 75% of surveyed physicians preferred 3 monthly doses followed by PRN dosing; or the treat (to dry) and extend approach. (DTX 2040.24). VEGF levels were known to be higher in DME compared to AMD, which was a further reason to use more doses at the outset to dry the macula. (Tr. 794:2-14 (Albini)). 2-8 monthly injections were used to start ranibizumab extended regimens. (DTX 2035.1). 3-6 initial 4-week/monthly injections were known for aflibercept extended regimens. (Tr. 804:9-22 (Albini); DTX 3198.1-2 (CRVO and DME studies); DTX 204.4 (CLEAR-IT 2 used 4 monthly doses before the extended dosing interval)).

These regimens thus were a known approach with a "finite number of identified, predictable solutions." *KSR*, 550 U.S. at 421.

Five monthly doses also "falls within a range disclosed in the prior art" of initial doses before an extended treatment interval. *Galderma*, 737 F.3d at 737. Dr. Albini confirmed as much. (*See, e.g.*, Tr. 783:1-784:1, 789:7-790:19 (Albini)). This "overlap in range establishes a *prima facie* case of obviousness," and a "presumption of obviousness," obligating Regeneron "to come forward with pertinent evidence that the overlapping range would not have been obvious in light of the prior art." *Genentech*, 946 F.3d at 1341. As with anticipation, Regeneron cannot meet this standard, because the DME Phase II clinical trial showed efficacy with just three monthly doses. (*See* Tr. 1235:12-20 (Chu 30(b)(6)) (using Phase II DME data utilizing three loading doses to guide Phase III design)). It picked 5 doses as a "compromise" to make it easier to run the Phase III trial, not to make the method work. (Tr. 1630:1-1632:8 (Chu) (five loading doses was a

"suggested compromise"); *see also* Tr. 1631:4-1632:8 (Chu) ("design consideration" compromise was attractive because it would not require a "substantial protocol amendment"); DTX 5385.6-7, 21 (emphasizing decisions based on protocol amendments and clinical endpoint timing)).

Dr. Csaky argued against a reasonable expectation of success under the theory that the clinical results were not "conclusive," and that "a little bit of … uncertainty" existed. (Tr. 1841:19, 1853:24 (Csaky)). "Conclusive proof of efficacy is not necessary to show obviousness" or to reach the threshold of a reasonable expectation of success. *Hoffmann*, 748 F.3d at 1331.

3. Secondary considerations do not save the claims here.

Regeneron has the initial burden of production of evidence on secondary considerations. Regeneron dropped its commercial success secondary considerations theory. (Dkt. 553).

For unexpected results, such results "must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006); *see also Abbott Lab'ys v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1345 (Fed. Cir. 2006). Dr. Csaky ***has not*** shown the claimed regimens produce outcomes that differ in kind versus monthly dosing or 3 monthly loading doses followed by 8 week dosing. Nor was it unexpected to need more doses at the outset. DME was known to be harder to treat, it is thus not surprising that some patients need more starting doses to get the macula dry. (Tr. 794:2-795:5 (Albini); DTX 2733.2).

Dr. Csaky admitted that his other secondary considerations were not tied to the use of aflibercept in the claimed DME or DR regimens. (Tr. 1925:15-1926:6 (Csaky)).

* * *

Thus, it required no great "leap" for a POSA to use 5 monthly doses followed by an 8 week interval for DME or DR. *Hoffmann*, 748 F.3d at 1333. The regimens in claim 25 of the '572 patent, and claims 11 and 19 of the '601 patent, are both obvious and obvious to try.

C. The Asserted Dosing Claims fail to comply with Section 112 requirements.

The Asserted Dosing Claims fail to enable the full scope of the claims; lack "blaze marks" required for written description; and leave a POSA with a lack of reasonable certainty about claim scope for the term "approximately." Dr. Stewart explained why the claims fail to comply with 35 U.S.C. § 112. (*See generally* Tr. 1270-1321). His opinions were largely unrebutted by Dr. Csaky. (*See generally id*. 1887-1913, 2005:14-22). Dr. MacMichael also explained the lack of written description support for "isotonic." (Tr. 1431:7-1432:6 (MacMichael)).

1. Claim 6 of the '572 patent fails to comply with Section 112.

Claim 6 covers a broad set of dosing regimens, directed to treating all angiogenic eye disorders. (PTX 3.25 (claim 6); Tr. 318:2-18, 322:5-11, 323:22-324:3 (Csaky); Tr. 1273:13-1275:22 (Stewart); Tr. 1888:14-1890:12 (Csaky)). The specification's column 5 angiogenic eye disorder list includes PVR, pannus, pterygium, and formed corneal neovascularization. (PTX 3.16; Tr. 1275:1-5 (Stewart); Tr. 1889:15-1891:4 (Csaky)). Dr. Stewart provided proof from the medical literature that anti-VEGF agents ***do not work*** for these diseases. (DTX 5429; DTX 5430; DTX 5431; Tr. 1276:12-1277:7, 1279:2-1281:23 (Stewart)). Thus, the specification fails, since "the patent's specification must enable a person skilled in the art to make ***and use the entire class***," and "the ***full scope*** of the invention as defined by its claims." *Amgen*, 143 S. Ct. at 1254 (emphasis added).

The regimen that Dr. Csaky, in response, argued would show aflibercept worked used ***4 daily doses*** delivered ***topically to the eye***, which is not the regimen that claim 6 requires. (Tr. 1987:21-1988:15 (Csaky); DTX 9031.1; Tr. 1985:19-1987:20, 1988:16-1990:25 (Csaky); DTX 9030 (subconjunctival injections); DTX 9032 (topical)). Dr. Csaky conceded that the literature that actually *injected* anti-VEGF compounds for PVR reported no useful result. (Tr. 1991:4-1993:2 (Csaky); DTX 5431.11; DTX 9033.1; DTX 9035.1). Claim 6 thus is not fully enabled.

Nor would a POSA accept that the written description showed Dr. Yancopoulos invented the claim 6 "isotonic" formulation. (Tr. 1431:7-1432:6 (MacMichael)). Dr. Yancopoulos even admitted that he "did not come up with that idea." (Tr. 213:21-214:3 (Yancopoulos)).

2. The 5 starting dose elements lack written description and enablement.

a. There are no blaze marks as written description requires.

"[O]ne cannot disclose a forest … and then later pick a tree out of the forest and say here is my invention. In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure." *Purdue*, 230 F.3d at 1326-27. Dr. Yancopoulos conceded that the specification tried to cover ***any*** dosing regimen where aflibercept might be effective. (Tr. 235:20-239:6 (Yancopoulos)). Having disclosed a forest; the specification required "blaze marks" to direct a POSA towards two specific "trees": five initial doses given at 4-week intervals, before proceeding to every 8-week dosing for (1) DME (PTX 3.25 (claim 25); PTX 1.21 (claim 11)); and (2) for DR (PTX 1.22 (claim 19)). (Tr. 1287:18-1301:17, 1319:16-1320:20 (Stewart); Tr. 1901:3-1908:5 (Csaky)). It gives none. (Tr. 1287:18-1297:19, 1300:2-20 (Stewart); Tr. 1887:9-1912:6, 2005:14-22 (Csaky)).

Example 7 did not cure this deficiency. It too has many options, and never links the specific five 4-week doses, followed by an 8-week dose regimen, to the specific DME and/or DR indications. (Tr. 1292:8-1310:2 (Stewart). Data and rationales Regeneron used to choose these 5 doses also is not in the specification. (Tr. 231:25-232:16 (Yancopoulos); *see also* Tr. 1235:5-20, 1632:9-1633:14 (Chu) (VIVID and VISTA data not in Examples, PANORAMA DR data is in DTX 19, her U.S. Patent No. 10,973,879 B2)). These claims thus lack proper written description.

b. Regeneron's obviousness arguments undermine both the "blaze marks" and enablement.

Regeneron's arguments about why the claimed regiments were not obvious to a POSA, if

accepted, render the specification non-compliant with 35 U.S.C. § 112. *See Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1380 (Fed. Cir. 2007) (warning patentees "beware of what one asks for," citing patentee's claim scope arguments to then find non-enablement). The specification is missing a specific regimen that combines all of the elements—the DME or DR indications, five doses at the 4-week interval before proceeding to the 8-week interval, justified by clinical data with that regimen. Regeneron insists that unique circumstances for diabetic patients discouraged POSAs from picking 5 monthly doses. (Tr. 1850:3-1851:24 (Csaky) (safety concerns with increased loading doses in diabetics); Tr. 158:8–159:10 (Yancopoulos) (safety concerns for "too much dosing or too high a dose" in DME patients)). But the specification never resolves these problems, confirming a lack of enablement and written description. (Tr. 1287:8-1292:7 (Stewart)).

3. The "approximately" term is indefinite.

"Definiteness is measured from the viewpoint of a person skilled in the art at the time the patent was filed." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 908 (2014) (cleaned up). "A claim is indefinite if its language might mean several different things and no informed and confident choice is available among the contending definitions." *HZNP Meds. LLC v. Actavis Lab'ys UT, Inc.*, 940 F.3d 680, 698 (Fed. Cir. 2019) (cleaned up). A POSA here faced multiple "approximately" standards, where the variability could be tied to days, weeks, or months; doctor or patient scheduling; or efficacy, with no clear standard to select. (Tr. 1312:13-1319:4 (Stewart); Tr. 1912:18-1913:17 (Csaky); Dkt. 494-9, 15 (Regeneron, proposing efficacy)).

Regeneron responded that other scientific publications use "approximately"—but that does not clarify *which* of these *multiple* standards apply. Dr. Stewart's own publication that Regeneron highlighted actually defined the scope of what qualified as "approximately," and used another, different measurement standard for the term. (Tr. 1354:12-1356:18 (Stewart); PTX 3348).

* * *

Thus, given the above, the claims fail to comply with 35 U.S.C. § 112 as well.

VII. THE ASSERTED FORMULATION CLAIMS ARE INVALID; THEY COVER KNOWN AND OBVIOUS FORMULATIONS, AND CLAIMED TOO BROADLY.

Like the dosing patents, Regeneron's Asserted Formulation Claims cover formulation ingredients known in the prior art (such as those found in Lucentis, Liu and Dix '226); while claiming broadly to cover subject matter that the named inventors did not fully describe or enable.

All '865 patent claims depend on Claim 1, and require a formulation with the anti-VEGF protein, aflibercept; "co-solvent";[5] buffer; and stabilizing agent ingredients; as well as various stability-related properties. (PTX 2.13, 19:29-41). The component categories, covered excipient recipes, pH and/or stability goals were not new for protein formulations. (Tr. 541:24-542:4 (Furfine); Tr. 2122:22-2123:11, 2125:15-2127:11 (Trout)). Using the same blueprint, Genentech had developed multiple prior art biologic formulations, including for the VEGF antagonist proteins bevacizumab and ranibizumab; and had made them stable for successful intravitreal administration. (Tr. 1026:19-1027:24, 1032:25-1039:6 (Rabinow); *see generally* DTX 726; DTX 2264; DTX 2265; DTX 3040; DTX 3510; DTX 5036; DTX 5037; DTX 5038; DTX 5040).

All Asserted Formulation Claims depend on Claim 2, which requires the "organic co-solvent" component to "comprise[] polysorbate," at a range of "about 0.03% to about 0.1% polysorbate 20" in claim 4; or "0.01% to 3% polysorbate 20" in claim 5. (PTX 2.13, 19:41-50). Regeneron did not invent this ingredient use or range. Regeneron first tried to develop a formulation *without* polysorbate, setting strict parameters that polysorbate levels were "not to exceed 0.01%." (DTX 711.1; Tr. 518:24-519:14 (Furfine)). That changed after Regeneron learned that Genentech's intravitreal formulations used polysorbate at a concentration that was five-times

[5] The evidence at trial demonstrated that Yesafili does not contain such a "co-solvent" as properly construed by the Court, which Defendants will demonstrate in their response brief and Defs.' FOF.

greater than Regeneron's maximum level. (Tr. 520:3-12 (Furfine); DTX 710; DTX 714; DTX 716.9). While Dr. Trout opined that no-one would apply one protein's formulation to a different drug substance (Tr. 2017:3-20), that is *exactly* what Regeneron did: it adopted Genentech's intravitreal buffer-stabilizer-polysorbate strategy for aflibercept. (Tr. 518:24-519:14 (Furfine)).

A. The Asserted Formulation Claims Are Anticipated.

1. Dix '226 (or iterations thereof) anticipates.

Dr. Rabinow confirmed that Dix '226 anticipates each and every element of the Asserted Formulation Claims. (Tr. 1053:7-1058:3, 1059:21-1064:2 (Rabinow)). Dr. Trout disagreed, on the theory that Dix '226's disclosed aflibercept protein range of 10 to 50 mg/mL was insufficient to teach 40 mg/mL specifically. (Tr. 2072:5-12 (Trout)).[6]

When the prior art discloses an overlapping range, it anticipates if "there is no reasonable difference in how the invention operates over the ranges." *Ineos*, 783 F.3d at 869. Since Defendants "established, through overlapping ranges, [of 10-50 mg/mL for their] prima facie case of anticipation," Regeneron must show the claimed 40 mg/mL "is critical to the operability" of the invention. *Genentech v. Hospira*, 946 F.3d at 1338 (quoting *Ineos*, 783 F.3d at 871).

The '865 patent's specification admits its "stable liquid ophthalmic formulation" invention covers an ***even broader*** range "that comprises 1-100 mg/mL VEGF-specific fusion protein antagonist." (PTX 2.4, 2:33-35). The '865 patent's "specific preferred embodiments" include 40 mg/mL *and* 50 mg/mL VEGF antagonist amounts, *and* a range of 40-50 mg/mL. (PTX 2.4-5,

[6] Regeneron will try to swear behind Dix '226 for this element, but the same disclosures in the 2005 priority application (DTX 8194) and the September 28, 2006 published application (DTX 4121) anticipate, as Defs.' FOF will explain. Regeneron did not corroborate a prior conception of what is claimed. (Tr. 1761:10-1764:11, 1766:22- 1767:10, 1768:11-1769:13 (Graham) (discussing DTX 900 and PTX 1825); Tr. 501:10-503:17, 532:5- 533:12 (Furfine) (discussing DTX 722 and DTX 725)). Nor did Regeneron properly disclose in discovery the documents and information it relied on for this purpose. Per the Court's instruction, Defendants will detail this in Defs.' FOF. (See Tr. 439:25-441:8, 1665:13-1670:20).

2:53-3:10). Nor did Dr. Trout opine that the 40 mg/mL concentration was critical to making the formulation work. (Tr. 2072:1-2074:4 (Trout)). Dr. Trout's other theories (*e.g.*, the Dix '226 formulation was lyophilized, Dix '226 covers another VEGF-Trap) fail for this same reason. (Tr. 2073:13-2074:4, 2075:4-17, 2076:6-9, 2077:1-4 (Trout)). The '865 patent also lists lyophilized formulations and this "other" VEGF as part of the invention. (PTX 2.4, 2:15-32).

B. The claims cover formulations that follow the Genentech Lucentis and/or Liu's established pathways, which would have been obvious to a POSA.

Formulators who worked with biologic molecules were well aware of the "major challenge that exists in the field of protein drugs," namely "formulations that maintain both protein stability and activity." (DTX 3610.13 [0003]). Again and again, a buffer, surfactant, and stabilizer were used to achieve a stable formulation. (*See* DTX 5036.1; 5037.1; 5038.2; 5040.1).

Dr. Trout admitted that the same classes and concentrations of formulation ingredients found in the '865 patent's Examples also correspond to the prior art:

Example 1 (vial)	Example 2 (vial)	Examples 3 (vial) & 4 (pre-filled syringe)	Examples 5 (vial) & 6 (pre-filled syringe)	Examples 7 (vial) & 8 (vial)	Shams DTX 0726.0032	Gaudreault DTX 2265.0002	Fraser DTX 0729.0002	Dix 226 DTX 0013.0007
50 mg/ml VEGF Trap, SEQ ID NO:4	50 mg/ml VEGF Trap, SEQ ID NO:4	40 mg/ml VEGF Trap, SEQ ID NO:4	40 mg/ml VEGF Trap, SEQ ID NO:4	20 mg/ml VEGF Trap, reconstituted to 40 mg/ml, SEQ ID NO:4	6 mg/ml 10 mg/ml ranibizumab	10 mg/ml 40 mg/ml ranibizumab	24.3 mg/ml VEGF Trap R1R2	50 mg/ml VEGF Trap SEQ ID NO:4
0.1% polysorbate 20	3% polyethylene glycol 3350	0.03% polysorbate 20	0.03% polysorbate 20	0.015% polysorbate 20	0.01% Polysorbate 20	0.05% Polysorbate 20	0.1% Polysorbate 20	0.1% Polysorbate 20
50 mM NaCl	50 mM NaCl	40 mM NaCl	135 mM NaCl	20 mM NaCl	None	None	100 mM NaCl	50 mM NaCl
10 mM phosphate	10 mM phosphate	10 mM phosphate	10 mM phosphate	5 mM phosphate	10 mM phosphate	10 mM succinate	5 mM phosphate 5 mM citrate	10 mM phosphate
5% sucrose	5% sucrose	5% sucrose	None	2.5% sucrose	100 mg/ml trehalose	10% trehalose	20% sucrose	20% sucrose
6.25	6.25	6.3	6.3	6.3	5.5	5.0	6.0	6.25

DTX 7066.0169 (Trout Resp. Report)

(Tr. 2141:24-2142:16 (Trout) (discussing DDX 9, above)).

1. Level of ordinary skill; scope and content of the prior art.

As noted in Section II, above, the parties largely agree on the POSA skill set. Regeneron

disputes that Dix '226 qualifies as prior art; Defendants met their burden to show that Dix '226 (directly or its published specification) is prior art. The references otherwise are not disputed as 35 U.S.C. § 102(b) prior art. (*See* Dkt. 494-12, 8-10).

2. The differences, if any, between the claims and the prior art.

a. Aflibercept (Fraser) + Lucentis formulation

Dr. Rabinow explained, without contradiction, that a POSA would know about the success of intravitreal Lucentis in humans, that aflibercept was one of the most potent anti-VEGF inhibitors tested, and that it had already been used in humans to target eye diseases. (*See* Tr. 1034:21-1037:21, 1042:9-1045:14, 1049:5-1050:4, 1050:10-15, 1050:21-1052:4 (Rabinow) (discussing Lucentis prior art, *e.g.*, DTX 726.32 (Shams), DTX 2265.2 (Gaudreault), and aflibercept art, *e.g.*, DTX 729.2 (Fraser) and DTX 2751 (Saishin))).

A POSA is motivated to replace one drug in a formulation with another in its class, particularly when the substitute drug has recognized advantages. *See Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483-84 (Fed. Cir. 1997) (it was obvious to replace acetaminophen in a formulation with the better pain reliever, ibuprofen); *Senju Pharm. Co. v. Lupin Ltd.*, 780 F.3d 1337, 1347 (Fed. Cir. 2015) (it was obvious to replace an eye formulation's fluoriquinolone drug with a more potent fluoroquinolone drug, gatifloxacin). It would have been obvious to a POSA to use Fraser's more potent aflibercept instead of ranibizumab in the Lucentis intravitreal formulation (Lucentis + Fraser). (*See* Tr. 1034:21-1037:21, 1042:9-1045:6, 1049:16-1052:4 (Rabinow) (discussing Lucentis prior art, *e.g.*, DTX 726.32 (Shams), DTX 2265.2 (Gaudreault), and aflibercept art, *e.g.*, DTX 729.2 (Fraser) and DTX 2751 (Saishin))).

b. Aflibercept (Fraser) + Liu to optimize the formulation.

A POSA trying to make a commercial product would want to optimize the existing injected Fraser aflibercept formulation recipe. (DTX 729; Tr. 1037:2-1039:6, 1065:4-18 (Rabinow)). It is

"not inventive to discover the optimum or workable ranges by routine experimentation." *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018).

A POSA knew from Fraser that Regeneron had already successfully formulated aflibercept *in vivo* at a concentration higher than Lucentis; and would look for other high concentration formulation precedents to optimize it. (Tr. 1023:4-24; 1025:8-1026:6 (Rabinow); DTX 729.2; DTX 730.35, [0279]-[0280]; DTX 13.7). A product for human use must be stable. (Tr. 1044:4-9 (Rabinow) (FDA-approved formulations must be stable)). Liu's strategies were designed to "overcome challenges of stability, viscosity, osmolarity and turbidity" for injectable formulations. (DTX 730.9 [0010]; Tr. 1023:3-1025:7 (Rabinow)). Liu's formulation components include buffers (*e.g.*, phosphate, histidine); stabilizers (*e.g.*, sorbitol); and surfactants (*e.g.*, polysorbate 20). (DTX 730.28, [0214] (buffers); DTX 730.29 [0216], [0219] (stabilizers and surfactants)). A POSA would prefer ingredients that had been used successfully in commercial products; optimizing those same ingredients found in previously-FDA approved biologic protein formulations would have been obvious to a POSA. (Tr. 1037:2-1039:6 (Rabinow)). It was obvious for a POSA to optimize Fraser's high-concentration aflibercept by following Liu.

c. Dix '226, alone or in view of the knowledge of a POSA.

As explained in Section VII.A.1. above, Dix '226 anticipates the claims, which alone renders them obvious.[7] *See Connell*, 722 F.2d at 1548.

Dr. Trout proposed that the '865 patent claims are not obvious because they specify the 40 mg/mL aflibercept drug concentration, and Dix '226 disclosed 10-50 mg/mL. (Tr. 2072:1-2073:18

[7] Dix '226 is prior art beyond 35 U.S.C. §102(e); nor did Regeneron meet its burden that Dix '226 qualifies for the 35 U.S.C. §103(c) exception. If Regeneron insists that Dix '226 formulations are not "suitable for intravitreal administration" (*e.g.*, based on an oncology use), then the evidence that Defendants presented at trial confirms Regeneron's failure to demonstrate that the '865 patent and Dix '226 were commonly owned. (*See* DTX 4956 and DTX 4986 (granting Sanofi rights in "VEGF Trap throughout the world"); Tr. 2183:19-2187:22 (Dr. Trout confirming he never reviewed Regeneron-Sanofi collaboration agreements)).

(Trout)). But "a change in … concentration" is "an unpatentable modification" absent proof of criticality, which is missing here. *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955).

3. Secondary considerations.

Since the '865 patent claims try to carve out a place within a known prior art range for the drug and formulation ingredients, they are presumptively prima facie obvious. *UCB, Inc. v. Actavis Lab'ys UT, Inc.*, 65 F.4th 679, 689-90 (Fed. Cir. 2023). "'[A]bsent a reason to conclude otherwise, a factfinder is justified in concluding that a disclosed range does just that—discloses the entire range.'" *Almirall, LLC v. Amneal Pharms. LLC*, 28 F.4th 265, 272 (Fed. Cir. 2022) (quoting *E.I. duPont*, 904 F.3d at 1008). Regeneron lacks evidence that "the 'prior art teaches away from the claimed range, … the claimed range produces new and unexpected results,' or other evidence demonstrates non-obviousness of the claimed range." *UCB*, 65 F.4th at 690.

Dr. Trout offered a hodgepodge of theories to argue teaching away, secondary considerations, or otherwise propose the '865 patent claims are non-obvious. (Tr. 2014:10-2017:3, 2041:19-2046:4, 2046:15-2054:24, 2060:15-2067:7, 2067:24-2069:24, 2071:23-2074:4, 2078:20-2079:10, 2079:22-2082:1, 2083:8-25, 2086:13-2087:17 (Trout)). None survive scrutiny, as Defs.' FOF will confirm in more detail. Dr. Trout's main theory—that a POSA would not intravitreally inject the larger molecule aflibercept, or at a high concentration—was debunked by March 2006, when Avery published successful human results with intravitreal bevacizumab. (DTX 2264.6). Avery recognized the small-molecule theory Dr. Trout relies on, but proposed that his larger dose, among other things, could explain why this small-molecule-retinal-penetration theory for ranibizumab did not lead to real-world failure when injecting bevacizumab intravitreally. (DTX 2264.8). Thus, "even if" the small-size theory "were initially enough to teach away from further development of" intravitreal aflibercept, it was "overcome" by the applicable priority date given this new published information. *Hoffmann*, 748 F.3d at 1333.

Nor is it credible to argue that a POSA lacked knowledge of the aflibercept structure from the prior art, a theory that the PTAB has already rejected. (DTX 4135.31-35).

Dr. Trout proposed safety concerns, side effects associated with intravitreal dosing, immune system triggers, a lack of Phase III clinical data showing retinal penetration, skepticism, and the like would discourage formulators. (Tr. 2034:2-20, 2040:6-2041:10, 2043:4-21, 2037:4-2038:8, 2063:1-24; 2080:7-2081:19). Yet, the '865 patent "provides no additional motivation to overcome th[ese] problem[s]" beyond the prior art. *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1373-74 (Fed. Cir. 2005); (Tr. 2123:23-2124:2 (Trout); Tr. 498:21-499:16 (Furfine)). This Court would "clearly err[] in finding any significant difference between the claimed invention" and the prior art based on such problems. *Merck*, 395 F.3d at 1373-74.

Dr. Trout also carefully blurred the claim scope when suggesting "unexpected results" and praise for "Eylea" were important secondary considerations for the '865 patent. (Tr. 2085:11-19, 2086:3-5; *see also* Tr. 2083:8-25 (unexpected aflibercept results); Tr. 2086:13-25 (unexpected lack of aflibercept side effects)). He failed to establish a nexus between the results or praise to the purported '865 patent invention (40 mg/mL concentration, stability measured by SEC). The same results and praise accurately apply to the aflibercept molecule and features in Regeneron's other patents. (Tr. 1432:19-1438:24 (MacMichael) (discussing prior art Regeneron patents and publications[8] that disclose and claim aflibercept, methods of making it, and treatment methods with aflibercept)). Regeneron's witnesses admitted that the properties of the aflibercept molecule drive clinical success. (Tr. 1794:9-19 (Graham); Tr. 184:12-185:7 (Yancopoulos)). Dr. Trout's opinion also conflicts with Regeneron's position before the PTAB, where Regeneron assigned the

[8] *See generally* DTX 7; DTX 2062; DTX 2730; DTX 3619; DTX 4116; DTX 4120; DTX 4229; DTX 4900; DTX 4903; DTX 8206; DTX 8207; DTX 8208; DTX 8209.

value of the extended interval dosing regimen and results to its other patents. (DTX 4135.16).

* * *

Given the above, the Asserted Formulation Claims encompass subject matter that would have been obvious to a POSA in view of the prior art.

C. The Asserted Formulation Claims Are Invalid Under Section 112.

The '865 patent fails to comply with 35 U.S.C. § 112, and the Asserted Formulation Claims are invalid for indefiniteness, lack of written description, and lack of enablement. The '865 patent fails to provide a POSA with reasonable certainty about how to qualify a formulation as "suitable for intravitreal administration," does not show the named inventors possessed any aflibercept formulation beyond those that were phosphate buffered and sucrose-stabilized; and does not enable the full claim scope. (Tr. 1416:19-1417:15 (MacMichael)).

1. "Suitable for intravitreal administration" is indefinite.

The phrase "suitable for intravitreal administration," like the phrases "aesthetically pleasing" or in an "unobtrusive manner," is "highly subjective and, on its face, provides little guidance to one of ordinary skill in the art." *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1371-72 (Fed. Cir. 2014); *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1350 (Fed. Cir. 2005), *abrogated on other grounds by Nautilus*, 572 U.S. 898 ("aesthetically pleasing" did "not notify the public of the patentee's right to exclude" because claim scope "would depend on the unpredictable vagaries of any one person's opinion"). Dr. MacMichael confirmed this. (Tr. 1417:9-15, 1429:20-1431:5). Dr. Furfine admitted the subjectivity (and uncertainty) of what excipients qualify as "suitable for intravitreal administration." (Tr. 543:24-545:2).

Subjective terminology cannot be salvaged when the specification lacks objective assessment standards. *Guangdong Alison Hi-Tech Co. v. Int'l Trade Comm'n*, 936 F.3d 1353, 1359-60 (Fed. Cir. 2019). None exist in the specification. (Tr. 2111:22-2113:10, 2114:5-15,

2115:16-2116:8 (Trout); *see also* PTX 2.2, 4, 6 at Title, Abstract, 1:45-52, 5:23-25 (no explanation of how or why to make a formulation suitable for intravitreal injection)).

Dr. Trout did "identify[] the components of the claimed invention that must be" in the intravitreal formulation (Tr. 2109:24-2110:25 (Trout)), but his list "does not suggest or provide any meaningful definition for the phrase [suitable for intravitreal injection] itself." *Datamize*, 417 F.3d at 1349. Dr. Trout suggested that Chang (PTX 1832) and Peyman (PTX 1758) would guide a POSA to "select excipients that have been used in marketed products with a relevant route of delivery." (Tr. 2113:8-10, 2114:5-22, 2115:16-23 (Trout)). That conflicts with his validity theory that presumes a POSA *cannot* incorporate formulation ingredients from a marketed drug, Lucentis, into an aflibercept formulation. (Tr. 2093:3-2095:18 (Trout)). The claims are indefinite.

2. The written description fails to show possession of the full claim scope.

For written description, when a patentee tries to claim a broader genus, the specification must convey with reasonable clarity to a POSA that the inventor was in possession of the entire claimed genus, not just a species of the genus. *Ariad*, 598 F.3d at 1350-51.

Dr. Trout conceded Dr. MacMichael's testimony that the Examples of the '865 patent are limited to one type of formulation—one where the buffer is phosphate, and the stabilizer is sucrose. (Tr. 1417:2-8, 1427:22-1428:9 (MacMichael); 2177:16-22, 2178:6-8 (Trout)). Dr. Trout argued that the specification gave sufficient common structural descriptions for the buffer and stabilizing agent categories beyond the Examples at column 2. (Tr. 2109:17-2110:25 (Trout); *see also* Tr. 2097:19-2099:18 (Trout) (discussing the supposedly limited set of buffers and stabilizers at column 2)). But that is precisely the problem—the column 2 disclosures are not limited to a discrete set of structures. (Tr. 1425:5:18 (MacMichael)). Column 2, lines 44-48 state that "the stabilizing agent ***may be*** sucrose, sorbitol, glycerol, trehalose, or mannitol; and the buffering agent ***may be, for example***, phosphate buffer." (PTX 2.4) (emphasis added). The '865 patent's use of

"may be" or "for example" keeps open, rather than closes, the structural scope of these terms.

3. Practicing the full claim scope imposes undue burdens on the POSA.

Patentees cannot game the system, prematurely patenting "inventions" bolstered by "little more than respectable guesses as to the likelihood of their success." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005). A specification cannot be just "a starting point" or "direction for further research"; it must provide "reasonable detail" to enable the ordinarily skilled artisan to practice the full scope of what was claimed. *See Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1284 (Fed. Cir. 2007). Moreover, "what is well known in the art ... is ... not a substitute for a basic enabling disclosure." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

Dr. MacMichael explained that the broad claim scope and limited number of Examples impose significant experimental burdens on a POSA under the factors of *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), and thus amounts to undue experimentation. (Tr. 1417:17-1418:2, 1419:13-1426:3, 1484:20-25 (MacMichael) ("It would require undue experimentation. It would require a significant amount of experimentation.")). Dr. Trout suggested that with the '865 patent specification in hand, the rest of the work for identifying useful, working, stable formulations would be routine. (Tr. 2097:16-2100:6, 2106:16-2108:4, 2109:6-9 (Trout)). That contradicts his non-obviousness testimony, where he insisted such variations required "a whole formulation study, a whole investigation," and that a POSA is "doing a whole research project at that point." (Tr. 2052:4-17 (Trout)). The claims are not enabled across the full claim scope.

VIII. CONCLUSION.

As shown above, and to be set forth in further detail for all claims and defenses in Defs.' FOF, the Asserted Claims here are anticipated; obvious; and invalid under 35 U.S.C. § 112.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on the 7th day of July, 2023, I served the foregoing "Defendants' Opening Post Trial Brief – Issues Where Defendants Bear The Burden of Proof" by electronically filing a true copy of the same with the Clerk of the Court using the CM/ECF system, which will send notice thereof to all counsel of record.

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