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

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

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

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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)
7-20-23 PTAB	*Celltrion, Inc. v. Regeneron Pharms., Inc.*, IPR2023-00462, Paper 11 (P.T.A.B. July 20, 2023)
AMD	Age-related macular degeneration
Asserted Patents	The '601 patent (PTX 1), '865 patent (PTX 2), and '572 patent (PTX 3)
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
BCVA	Best corrected visual acuity
DA VINCI	Phase II Regeneron clinical trial for the use of aflibercept to treat DME
Defs.' FOF, Defendants' Proposed Findings	Defendants' Proposed Findings of Fact and Conclusions of Law (Dkt. 587)
Defendants	Biocon Biologics Inc. and Mylan Pharmaceuticals Inc.
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
Dosing Patents	The '572 patent and the '601 patent
DR	Diabetic retinopathy
FDA	United States Food and Drug Administration

Abbreviation	Description
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)
Liu	US. Patent Application Publication No. 2004/0197324 A1 (DTX 730)
mg	Milligram
mL	Milliliter
POSA	Person of ordinary skill in the art
PRN	*Pro re nata* or as-needed dosing
PTAB	Patent Trial and Appeal Board
PVR	Proliferative vitreoretinopathy
Regeneron	Regeneron Pharmaceuticals, Inc.
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)
Saishin	Yoshitsugu Saishin et al., *VEGF-TRAP$_{R1R2}$ Suppresses Choroidal Neovascularization and VEGF-Induced Breakdown of the Blood-Retinal Barrier*, 195 J. CELLULAR PHYSIOLOGY 241 (2003) (DTX 2751)
Tr.	Trial Transcript
VEGF	Vascular endothelial growth factor
VEGF Trap	Regeneron development name for aflibercept
VIEW 1/VIEW 2	Phase III Regeneron clinical trials for the use of aflibercept to treat AMD

TABLE OF RECORD CITATIONS

Abbreviation	Description
Dkt. 427	Order on Claim Construction (April 19, 2023)
Dkt. 432-17	Opening Expert Report of Bernhardt L. Trout, Ph.D., with Appendices A and B, dated February 2, 2023
Dkt. 432-18	Reply Expert Report of Bernhardt L. Trout, Ph.D., Appendices A and B, dated March 30, 2023
Dkt. 433	Regeneron's Stipulation Regarding Summary Judgment and Case Narrowing (April 27, 2023)
Dkt. 445-17	Response Expert Report of Dr. Bernhardt L. Trout, dated March 2, 2023
Dkt. 584	Regeneron's Responsive Post-Trial Brief (July 24, 2023)
Dkt. 587	Defendants' Proposed Findings of Fact and Conclusions of Law (July 24, 2023)

Regeneron's asserted claims are invalid, as Defendants' Proposed Findings (Dkt. 587) and prior briefing detail. What the Dosing Patent claims cover was inherent (in Dixon's clinical trial 2 mg dose, in a comfortable and non-irritating formulation, in a press release's PRN dosing regimen) and obvious (an isotonic formulation, 5 loading doses). The specification fails under § 112 for angiogenic eye disorders, isotonicity, and 5 loading doses, while using uncertain claim terms ("approximately"). The '865 patent claims are anticipated by Dix '226 (which is prior art; and its teachings, examples, and embodiments disclosed what is claimed), obvious over Dix '226 or combinations (Fraser + Lucentis, Fraser + Liu); and invalid for claiming a broad genus from limited examples, and using the indefinite phrase "suitable for intravitreal administration."

I. THE DOSING PATENTS.

A. Claim 6 – the isotonic solution is anticipated by Dixon (DTX 204).

Dixon describes clinical trials with the claimed dosing regimen at 2 mg of aflibercept. (Dkt. 584, 24-25). That 2 mg dose was Regeneron's Eylea®, and had the property of being isotonic. Regeneron wrongly insists a POSA must know this inherent property "before the priority date." (*Id.*, 24). But a reference anticipates "even when the relevant properties of the thing disclosed were not appreciated at the time." *Abbott Lab'ys v. Baxter Pharm. Prods., Inc.*, 471 F.3d 1363, 1367 (Fed. Cir. 2006). At the time, a POSA knew that Phase 3 trials test the product for commercial marketing. (Tr. 827:17-25 (Albini)). Over 220 retinal practices across 43 U.S. states had access to the Eylea® formulation via the Phase 3 trials.[1] Dixon also listed three criteria for the aflibercept formulation: (1) "comfortable;" (2) "non-irritating;" ***and*** (3) for "direct injection into the eye." (DTX 204.3). The "non-isotonic" formulations Regeneron relies on at most meet the last; *only* an isotonic formulation meets all three. (Tr. 1096:15-1098:8 (Rabinow); DTX 3588.11,

[1] (DTX 231.3-7 (listing the states with participating sites); *see also* PTX 188.1 (noting "we cannot significantly increase the number of sites beyond the 220 or so already assumed" in the U.S and Canada)).

13). A non-isotonic formulation can injure eyes—the antithesis of comfortable and non-irritating. (Tr. 1098:9-1099:10, 1173:6-13 (Rabinow); DTX 9038.2 (non-isotonic ziv-aflibercept may cause retinal toxicity and detachment)). A POSA knows a harmful formulation is not put to Phase 3 clinical trials. The isotonic solution thus was inherent[2] and known. Dixon anticipates claim 6.

B. Claim 6 – using an isotonic solution would have been obvious.

Defendants focused on "isotonic" because the obviousness test *requires* considering "the differences between the prior art and the claims at issue." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 399 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)). Regeneron admits Dixon taught the claim 6 regimen (Dkt. 433), arguing "the only claim limitation it [expressly] lacks is" isotonic; thus, that limitation received "the prominence that it must" in Defendants' analysis. *Warner Chilcott Co., LLC v. Teva Pharms. U.S.A, Inc.*, 642 Fed. App'x 996, 1002 (Fed. Cir. 2016).

Dixon gave a POSA a reason to pursue the claimed regimen and dose (it was in clinical trial human use), and the injected dose's properties—comfortable and non-irritating. (DTX 204.3-4). An isotonic formulation is obvious and "obvious to try" because only it meets Dixon's criteria. Even if the options include hypertonic and hypotonic formulations, it remains a preferred 1 of a limited 3 options. (Tr. 212:14-24 (Yancopoulos)). Hecht confirms why an isotonic formulation also meets the criteria. (DTX 3588.11, 13). Regeneron does not contest this. (Dkt. 584, 25-27).

Regeneron argues this is not viewing the claims "as a whole." (Dkt. 584, 26). Finding a regimen a POSA is motivated to consider, then how to dose the regimen, is a proper path to show obviousness. *See In re Copaxone Consol. Cases*, 906 F.3d 1013, 1025-29 (Fed. Cir. 2018); *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1332 (Fed. Cir. 2014). Dixon described an *actual* regimen in human clinical use. (DTX 204.4). It is a "design step well within the grasp

[2] Dr. Trout did not opine on inherency in his expert reports. (*See generally* Dkt. 432-17, 432-18, 445-17). Regeneron is prohibited from using him for that purpose here.

of a person of ordinary skill in the relevant art." *KSR*, 550 U.S. at 427. The claims have no efficacy requirements. (Dkt. 427, 26-28). Defendants need only prove a "suitable" regimen and dose, *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1197-98 (Fed. Cir. 2014), not those superior to Lucentis or the "most effective." (Dkt. 584, 26).

Even so, POSAs expected the Phase 3 trials would hit the primary endpoint and have a better interval compared to Lucentis. VIEW 1 clinician Dr. Nguyen, (DTX 2053.13), in 2010 explained the 4- and 8-week arms were designed "to get the maximum result;" the dose would "most likely have a longer duration of action," and it was expected that "every eight weeks let's just say to be conservative work as well as every four weeks of Lucentis," which would make it "a winner." (DTX 2053.17). Dr. Rosenfeld also opined it would be the "duration of effect that really shows the benefit." (DTX 2053.18; *see also* DTX 917.1). Nor were the clinical results unexpected given the robust Phase II results seen in Dixon, showing patients gaining an average of 9 BCVA letters and 29% gaining ≥ 15 letters, on a regimen that involved even fewer doses than the claimed regimen. (Tr. 840:15-844:23 (Albini); DTX 204.4; DTX 3173.6, 9, 12, 16 19).

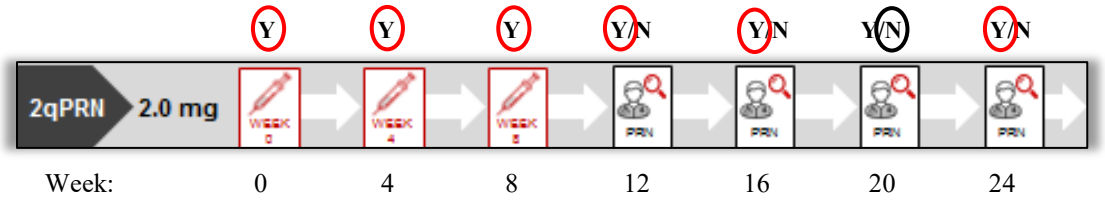
Dr. Csaky's so-called "praise" was a routine press release announcing the FDA approved the drug, (DTX 3112.1), for the *expected* outcome. Dr. Albini viewed the claim as a whole to show that Dixon's disclosed claim 6 regimen and formulation guidance taught isotonicity. (Tr. 811:13-813:12; 826:7-23 (Albini); DTX 204.4). Industry never praised the isotonic solution in the regimen. (Tr. 845:1-18; 846:12-15 (Albini)). Claim 6 was obvious.

C. The DME/DR claims are anticipated.

Regeneron's DME/DR claims lack any limitations that Regeneron raises against the prior art.[3] (Dkt. 584, 18; PTX 3.25, claim 25; PTX 1.21, claim 11; PTX 1.22, claim 19).

[3] Dr. Csaky argued the art did not reduce office visits; fully fix the regimen; was not "reliable," etc. (*See, e.g.*, Tr. 293:25-295:2, 1816:4-24, 1824:1-19, 1849:22-25, 1914:18-1915:6, 1915:21-1916:4 (Csaky)).

Regeneron cites *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008); it is distinguishable. (Dkt. 584, 18). Those claims had a 5-step secured transaction process in a precise order; the prior art had two distinct protocols. *Id.* at 1363, 1368-69. The two protocols the prior art deliberately kept distinct could only be combined for obviousness, not anticipation. *Id.* at 1371. Here, the Press Release has *one* regimen, the PRN regimen, which includes the 5 loading dose option plus 8-week interval *within* its existing range:



(PDX 1.124; Tr. 1958:19-1961:24 (Csaky) (conceding the regimen that meets the claims in the above)). The order of the protocol thus is as arranged as in the claim. Defendants' experts did not accept Regeneron's contrary arguments.[4] Regeneron argues that a POSA could not know PRN visits would occur monthly. (Dkt. 584, 20). A POSA understands that PRN dosing uses monthly visits. (Tr. 782:8-10 (Albini); *see also* DTX 915.8 (subjects in Regeneron trials being evaluated monthly); Tr. 227:3-228:8 (Yancopoulos) (clinical trials require monthly visits no matter the regimen)). A POSA also knows clinical trial arms are on the same schedule to mask who gets which dose. (Tr. 1233:8-1234:7 (Chu(30(b)(6)) (discussing maintaining the mask); Tr. 1591:8-1592:6 (Chu) (sham injections as another part of the mask)). Here it was every 4 weeks. (DTX 3198.2). Dr. Do also published that patients were seen every 4 weeks/monthly in the trial. (DTX 3105.2-3). Further, Dr. Csaky's invalidity position (PRN regimens do not invalidate) and infringement opinions (a PRN regimen might infringe) conflict. (Tr. 416:13-17 (Csaky)). The claims cannot "be twisted one way to avoid anticipation and another to find infringement."

[4] Dr. Stewart *did not* admit the press release PRN regimen lacked 5 loading doses; he confirmed the disclosed PRN regimen permits a 5-dose/8-week method for patients. (Tr. 1358:20-1359:5 (Stewart)).

Amazon.com, Inc. v. Barnesandnoble.com, Inc., 239 F.3d 1343, 1351 (Fed. Cir. 2001).

Regeneron argues that DR is not a genus to the DME species; that contradicts its representations to FDA. (PTX 3332.3-4). FDA gave Regeneron "breakthrough designation" for DR *in DME patients*, because they are a subset of DR patients. (PTX 3332.35-36). FDA did not accept the reverse—that the same data supports treating DR patients *without* DME. (PTX 3332.35).[5] Dr. Albini confirmed that "DME is technically a type of diabetic retinopathy," namely "a complication of diabetic retinopathy or a subtype of diabetic retinopathy," (Tr. 779:6-22 (Albini)), thus treating DME treats a type, complication, or species of DR.

D. The DME/DR claims would have been obvious.

Defendants did not simply "assume without basis" that it was obvious to treat all DR patients with *every* method to treat DME. (Dkt. 584, 24). Defendants proved that DME patients are a "species" of DR patients; since claim 19 covers a method of treating the DR "genus," that is anticipated by, and obvious over, the same method for treating DME. *In re Kubin*, 2007 WL 2070495, at *4 (P.T.A.B. May 31, 2007), *aff'd*, 561 F.3d 1351, 1361 (Fed. Cir. 2009) ("A single, obvious species within a claimed genus renders the claimed genus unpatentable under § 103.").

E. Regeneron continues to blur lines on secondary considerations.

The Phase 3 VIEW 1/VIEW 2 results were not unexpected; Regeneron publicized those "successful[]" results *before* the patents were filed. (*See generally* DTX 917; DTX 915; DTX 2053). Success was also expected for the 8-week DME regimen. Dr. Rosenfeld stated that after seeing the 6-month DA VINCI data for DME (the data from the Press Release's regimen), "I said wow, dosing every two months with VEGF-Trap and diabetic macular edema is as good as

[5] This is why the full scope of DR uses is not enabled (because the full scope of the DR disease includes types of patients not experiencing DME, (*see* Tr. 1287:2-7 (Stewart)), but *is* anticipated by the DR in DME patient species; once the prior art "discloses a point within the claimed range, the prior art anticipates the claim." *UCB, Inc. v. Actavis Lab'ys UT, Inc.*, 65 F.4th 679, 687 (Fed. Cir. 2023).

monthly dosing … I thought wow that's a winner." (DTX 2053.18-19). The results were not unexpected, did not satisfy a long-felt need, or solve others' failures. (Dkt. 587, 160-68). Copying further is not "probative of nonobviousness," since "a showing of bioequivalence is required for FDA approval." *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013). (Tr. 790:22-793:10 (Albini); DTX 3102.1, .5; DTX 2733.1-2).

F. The claims are invalid under 35 U.S.C. § 112.

Regeneron argues Dr. Stewart wrongly required proof of specification examples. (Dkt. 584, 29). He ***did not*** assume the wrong standard for his testimony. (Tr. 1358:5-8 (Stewart)).

Isotonic. A POSA did not have common structural features or properties for "isotonic" from the specification. Dr. Yancopoulos *disagreed* a physiological saline formulation with the structural features Dr. Trout relies on is isotonic. (Tr. 181:19-25 (Yancopoulos)). He argued only a formulation identical to the eye's was isotonic; which differs from Dr. Graham's standard (300-320 mOsm); both differ from Dr. Trout's. (*Compare* Tr. 139:14-140:13 (Yancopoulos), *and* Tr. 1721:23-24 (Graham), *with* Tr. 640:20-642:4 (Trout)). Under the "isotonic" standards of Yancopoulos/Graham, YESAFILI™ does not infringe. Nor did Dr. Trout find "blaze marks" to combine the isotonic solution from the myriad of formulations disclosed (emulsion, oily medium; non-isotonic solutions, etc.) with the specific regimen claimed.

Angiogenic eye disorder. When a 2022 reference explains that "a pharmacologic method of inhibiting PVR remains elusive," (DTX 5430.7); or physicians must dose the drug four times daily, (DTX 9031.1-2); or move injection sites to better target the disease, (DTX 5429.1); that shows the claim 6 dosing regimen, at the time of filing, did not work across the full claim scope absent an undue experimental burden. Regeneron could have shown that a POSA could as a matter of routine exclude the inoperative embodiments, but did not, and thus the claims are invalid. *Crown Ops. Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1380-81 (Fed. Cir. 2002).

DME/DR: no written description. The specifications lack the 5-dose regimen species "arranged as in the claim." (*See* Dkt. 584, 18). The lists of "preferred" methods and materials starting at column 3 never lead to the claimed DME or DR regimen; it's buried in a million possibilities to combine.[6] Example 7 does not tie any of its laundry list of regimens to a specific disease state, let alone DR. (*See* Tr. 1292:25-1294:9, 1296:14-18, 1297:2-19 (Stewart)). The working Example for DME lists the same Press Release regimens that Regeneron insists teach away from 5 loading doses. (Tr. 1846:11-1847:3, 1848:8-1849:2, 1958:19-1961:24 (Csaky)). From this, a POSA sees the forest; not the tree.

DME/DR: no enablement. Whether a POSA "could" make injections into the eye is not dispositive of whether he believes he should. Regeneron's obviousness defense insists there is "no indication" in which a POSA would "accept without question" the use of 5 loading doses. The specifications here lack the data and reasoning Dr. Csaky insists a POSA would need to pursue 5 loading doses; and contains the same data Dr. Csaky argues discourages using 5 loading doses. (Tr. 1846:11-1847:3, 1848:8-1849:2 (Csaky)). This precludes enablement. *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005). This also distinguishes *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1310 (Fed. Cir. 2015); there the prior art taught that BAK would not increase permeability; the specification's test data resolved this to show it did.

Approximately is indefinite. *Andrew Corp. v. Gabriel Elecs., Inc.*, 847 F.2d 819, 821-22 (Fed. Cir. 1988) allowed "closely approximate" because the technology "could not reasonably be expressed more precisely." Regeneron touts its regimens as "fixed," thus should not need approximation. *Immersion Corp. v. Motorola Mobility LLC*, 2018 WL 5294508, at *7 (D. Del.

[6] (*See* PTX 1.13, 5:21-39 (listing angiogenic eye disorders); PTX 3.16, 5:30-48 (same); PTX 1.13-14, 6:25-7:44 (describing dosing routes, ranges, and injection numbers); PTX 3.16-17, 6:35-7:52 (same); *see also* Tr. 1271:23-1272:7, 1280:24-1281:3, 1283:2-16 (Stewart))

Oct. 25, 2018) just pushed the indefiniteness issue to summary judgment; in *Parker Compound Bows, Inc. v. Hunter's Mfg. Co., Inc.*, 2016 WL 617464, at *23 (W.D. Va. Feb. 12, 2016), the specification "describe[d] how" the term approximated "is measured." The Dosing Patents defined "about" to mean "no more than 1%" variation. (PTX 1.12, 3:14-23; PTX 3.15, 3:24-32). It lacks a comparably-defined standard for "approximately."[7] Thus, the claims are indefinite.

II. THE '865 FORMULATION PATENT.

The asserted '865 claims blazed no new trail—they follow Dix '226; Fraser + Lucentis; and Fraser + Liu. Regeneron complains these references lack one example combining 40 mg/ml, glycosylated aflibercept, buffer, stabilizing agent and polysorbate to achieve 98% native conformation. (Dkt. 584, 4). But applying Regeneron's logic, ***so does the '865 patent***, which never states the Example VEGFs are glycosylated, never injects the formulation, never shows lack of inflammation, and is silent on efficacy. These claims are not new, and are also obvious.

A. Dix '226 anticipates and renders the claims obvious.

Regeneron lacks evidence of a pre-filing date conception of, or testing across, the full claim scope. *Oka v. Youssefyeh*, 849 F.2d 581, 584 (Fed. Cir. 1988) (conception of a species inadequate to support the generic count); *Estee Lauder Inc. v. L'Oreal, S.A.*, 129 F.3d 588, 594-95 (Fed. Cir. 1997) (when tests are in the claims, there must be "appreciation that the tests were successful"). It also cannot support its claims with its provisional application given the new matter added. (Dkt. 587, 326-28). Thus, Dix '226 (or its publication, DTX 4121) is prior art, at least under § 102(a); hence avoiding § 103(c) prohibitions. (*See* Dkt. 587, 325-29, 422-52).

Regeneron argues there is no overlap with its 40 mg/mL element; or disclosure of 98%

[7] The art Regeneron cites applies different ranges even when applied to days. (*See* Tr. 1343:23-1349:22, 1353:23-1354:11 (approximately used consistently in cited art, not in multiple ways like in the Dosing Patents)). Regeneron at trial also defined the term differently to mean schedule ranges or efficacy outcomes. (Tr. 1312:24-1313:22, 1315:2-22, 1316:19-1317:14 (Stewart)).

native conformation. (Dkt. 584, 3-4, 12-13). Dix '226 used "specific embodiment" and "preferred" guidance to narrow the scope to a limited set, including 40 mg/mL. *In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962). Dix disclosed "a specific embodiment" of "SEQ ID NO:4" that "is glycosylated" at the same asparagine residues (DTX 13.6, 5:37-42), and preserved the native conformation of 98% at both higher and lower concentrations, rendering it "a natural result of the formulation ingredients," as the PTAB recently observed. (Ex. 1, *Celltrion, Inc. v. Regeneron Pharms., Inc.*, IPR2023-00462, Paper 11, 20-21, 31-32 (P.T.A.B. July 20, 2023) ("7-20-23 PTAB"); *see also* Tr. 2148:17-2150:5 (Trout) (Dix's 50 mg/mL formulation was stable and not aggregating; the 40 mg/mL would be as well)). Dix '226 also overlaps with the claims viewed *as a whole*, with buffers, stabilizers, co-solvents, and the like. Dix '226 anticipates.

B. The combinations: Fraser + Lucentis or Fraser + Liu.

The PTAB also recently rejected the arguments Dr. Trout made about Fraser. The PTAB stated Fraser was "one clear starting point" for formulations; disclosed the VEGF $Trap_{R1R2}$ sequence; taught preparing aflibercept in CHO cells; and was the Dix '226 Example 5 formulation, and hence inherently stable with the proper native conformation. (7-20-23 PTAB at 28-33, 38-39; DTX 13.9 (Dix Table 9 shows native confirmation)). The '865 patent admits CHO cell synthesis produces glycosylated structures. (PTX 2.6, 6:32-37).

Saishin (DTX 2751) showed one more-potent aflibercept "markedly suppressed" VEGF (Tr. 1080:6-18 (Rabinow); DTX 2751.7). Dr. Trout insists a POSA would want lower, non-intravitreal doses with ranibizumab. (Tr. 2033:14-20, 2072:21-2073:6 (Trout)). That is not credible. At the time clinicians thought aflibercept had "a better probability" to show a more durable treatment effect," and encouraged Regeneron to *increase* doses to "2 mg and 4 mg." (DTX 222.1). In the intravitreal injection volume, those doses are 40 mg/mL and 80 mg/mL; Gaudreault used 40 mg/mL. (Tr. 1645:3-15; 1650:3-25 (Chu); Tr. 1033:10-19, 1035:4-24, 1072:23-1073:4

(Rabinow); DTX 2264.2; DTX 9036.6; DTX 726.32; DTX 2265.2). Dr. Trout's teaching away theories for Gaudreault also are not credible. The field intravitreally dosed the much-larger bevacizumab, at higher doses (1.0/1.25 mg), to good results. (DTX 3058.1; DTX 2264.1; 9036.5). Regeneron moved aflibercept, not mini-Trap, to human trials. (Tr. 548:13-22 (Furfine); DTX 4957.5). The Eylea® formulation was not unexpectedly safer—Regeneron told FDA it ***also*** had "transient ocular inflammation." (PTX 3255.4, 19; Tr. 546:25-548:12 (Furfine)).

C. Other secondary considerations.

Dr. Trout's "unexpected results" analysis comparing to Lucentis conveniently avoids a true apples-to-apples formulation comparison; prior art aflibercept formulations can also deliver the benefit of aflibercept's longer half-life that produces extended dosing. (*See* DTX 2053.6). There is no "safety" claim element, which precludes nexus; nor can Regeneron assign the same secondary consideration benefits to all its patents here. Regeneron conceded no commercial success; YESAFILI™ did not copy what the named inventors actually made. (Tr. 545:3-6 (Furfine); Tr. 2178:6-8 (Trout); *see also* Tr. 1427:22-1428:5 (MacMichael)).

D. The claims fail to comply with § 112.

Regeneron offered multiple POSA standards for intravitreal "suitability" that change the claim scope; and no reasonably certain standard in the specification. (Dkt. 587, 398-406). The term is indefinite. For enablement and written description, Regeneron insists the formulations can be prepared; if so, they are obvious. If a POSA must resolve teaching away; or cannot combine a Lucentis formulation with aflibercept without more guidance, the specification imposes an undue experimental burden, and lacks written description. (*See* Dkt. 587, 406-21).

III. CONCLUSION.

As shown in Defendants' opening and responsive brief, above; and in Defs.' FOF, the Asserted Claims here are anticipated, obvious, and invalid under 35 U.S.C. § 112.

Respectfully submitted,

Date: July 28, 2023

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CERTIFICATE OF SERVICE

I hereby certify that, on the 28th day of July 2023, I electronically filed the foregoing "Defendants' Reply Post Trial Brief – Issues Where Defendants Bear the Burden of Proof" with the Court's CM/ECF system, which will send notification of the same to all counsel of record.

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EXHIBIT 1

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Paper 11
Date: July 20, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2023-00462
Patent 10,464,992 B2

Before JOHN G. NEW, SUSAN L. C. MITCHELL, and JAMIE T. WISZ, *Administrative Patent Judges.*

WISZ, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Celltrion, Inc. ("Petitioner") filed a Petition (Paper 2, "Pet.") requesting an *inter partes* review of claims 1–18 of U.S. Patent No. 10,464,992 (Ex. 1001, "the '992 patent"). Regeneron Pharmaceuticals, Inc. ("Patent Owner") filed a Preliminary Response (Paper 6, "Prelim. Resp."). With Board authorization, Petitioner filed a Pre-Institution Reply (Paper 9, "Reply"), and Patent Owner filed a Sur-Reply (Paper 10, "Sur-Reply").

Under 35 U.S.C. § 314(a), the Board "may not authorize an *inter partes* review to be instituted unless . . . the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." After considering the Petition, the Preliminary Response, the Reply, the Sur-reply, and the evidence of record, we determine that Petitioner has demonstrated a reasonable likelihood of prevailing with respect to at least one claim challenged in the Petition. Accordingly, we institute an *inter partes* review of claims 1–18 of the '992 patent, based on all of the grounds identified in the Petition. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1354, 1359–60 (2018); 37 C.F.R. § 42.108(a) ("When instituting post-grant review, the Board will authorize the review to proceed on all of the challenged claims and on all grounds of unpatentability asserted for each claim.").

The following findings of fact and conclusions of law are not final, but are made for the sole purpose of determining whether Petitioner meets the threshold for initiating review. Any final decision shall be based on the full trial record, including any response timely filed by Patent Owner. Any arguments not raised by Patent Owner in a timely-filed Response may be deemed waived, even if they were presented in the Preliminary Response.

II. BACKGROUND

A. Real Parties-in-Interest

Petitioner identifies Celltrion, Inc., Celltrion Healthcare Co. Ltd. and Celltrion Healthcare U.S.A., Inc. as the real parties-in-interest. Pet. 39. Patent Owner identifies Regeneron Pharmaceuticals, Inc. as the real party-in-interest. Paper 4, 1.

B. Related Matters

The parties identify the following district court litigation involving the '992 patent: *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, Case No. 1-22-cv-00061 (N.D.W.V), filed on August 2, 2022. Pet. 39; Paper 4, 1.

The parties identify two matters related to the '992 patent filed at the USPTO: (1) *ex parte* reexamination Control No. 90/014,448 (pending); (2) *Chengdu Kanghong Biotechnology Co., Ltd. v. Regeneron Pharms., Inc.*, IPR2021-00402 (PTAB Jan. 7, 2021) (terminated). Pet. 39; Paper 4, 1.

Patent Owner identifies other *inter partes* review proceedings challenging related patents. *See* Paper 4, 1–3. The pending proceedings (excluding joined cases) include:

Mylan Pharms. Inc. v. Regeneron Pharms., Inc., IPR2021-00880, challenging claims of U.S. Patent No. 9,669,069 B2, Final Written Decision (Paper 89) issued Nov. 9, 2022;

Mylan Pharms. Inc. v. Regeneron Pharms. Inc., IPR2021-00881, challenging claims of U.S. Patent No. 9,254,338 B2, Final Written Decision (Paper 94) issued Nov. 9, 2022;

Mylan Pharms. Inc. v. Regeneron Pharms., Inc., IPR2022-01225, challenging claims of U.S. Patent No. 10,130,681 B2, Institution Decision (Paper 21) issued Jan. 11, 2023;

Samsung Bioepis Co. Ltd. v. Regeneron Pharms., Inc., IPR2023-00442, challenging claims of U.S. Patent No. 10,130,681 B2, petition filed Jan. 6, 2023;

Mylan Pharms. Inc. v. Regeneron Pharms., Inc., IPR2023-00099, challenging claims of U.S. Patent No. 10,857205 B2, Decision Denying Institution (Paper 10) due to statutory disclaimer issued Mar. 1, 2023;

Mylan Pharms. Inc. v. Regeneron Pharms., Inc., IPR2022-01226, challenging claims of U.S. Patent No. 10,888,601 B2, Institution Decision (Paper 22) issued Jan. 11, 2023; and

Apotex, Inc. v. Regeneron Pharms., Inc., IPR2022-01524, challenging claims of U.S. Patent No. 11,253,572 B2, Decision Denying Institution (Paper 9) issued Mar. 10, 2023. *Id.*

Finally, Patent Owner lists the following pending applications as related to the '992 patent: U.S. Patent Application Nos. 17/072,417, 17/112,404, 17/112,063, and 17/350,958. *Id.*

C. The '992 Patent

The '992 patent is titled "VEGF Antagonist Formulations Suitable for Intravitreal Administration." Ex. 1001, code (54). The '992 patent is directed to pharmaceutical formulations containing a vascular endothelial growth factor ("VEGF") antagonist. *Id.* at 1:30–34. The '992 patent defines the term "VEGF antagonist" as a "compound capable of blocking or inhibiting the biological action of [VEGF], and includes fusion proteins capable of trapping VEGF." *Id.* at 6:9–12. The '992 patent refers to such a fusion protein as a "VEGF trap" and discloses that it comprises "an

immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component." *Id.* at 2:7–11. "In specific embodiments, the VEGF antagonist is expressed in a mammalian cell line such as a [Chinese Hamster Ovary ("CHO")] cell and may be modified post-translationally." *Id.* at 6:14–16.

According to the '992 patent, "[p]roteins possess unique chemical and physical properties that present stability problems: a variety of degradation pathways exist for proteins, implicating both chemical and physical instability." Ex. 1001, 5:37–40. In one embodiment, the '992 patent describes "a stable pharmaceutically acceptable formulation comprising a VEGF antagonist." *Id.* at 6:41–54. "The formulation can also comprise one or more pharmaceutically acceptable carriers, buffers, tonicity agents, stabilizers, and/or excipients." *Id.* at 6:47–49. "An example of a pharmaceutically acceptable liquid formulation comprises a VEGF antagonist . . . , a buffer, an organic co-solvent such as polysorbate, a tonicity agent such as NaCl, and optionally, a stabilizer such as sucrose or trehalose." *Id.* at 6:49–54.

The '992 patent provides eight examples of VEGF Trap formulations and their corresponding stability test data. *See* Ex. 1001, 8:8–12:30. Examples 1–4 describe liquid formulations include varying amounts of VEGF Trap (SEQ ID NO: 4), phosphate, NaCl, polysorbate 20 or polyethylene glycol, and sucrose. *See id.* at 8:8–9:55. Examples 1–4 further disclose that the formulations contain at least 98% of VEGF Trap present in native configuration following storage at 5° C for two months as measured by size exclusion chromatography ("SEC"). *See id.*

D. Challenged Claims

Petitioner challenges claims 1–18 of the '992 patent. Pet. 1. Claims 1 and 10, which are the independent claims of the '992 patent, are illustrative of the challenged claims and are reproduced below, with the only difference being claim 1 describes a vial comprising a formulation and claim 10 describes the formulation.

> 1. A vial comprising:
>
> a vascular endothelial growth factor (VEGF) antagonist,
>
> an organic co-solvent,
>
> a buffer, and
>
> a stabilizing agent,
>
> wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and
>
> wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.

Ex. 1001, 19:31–43.

> 10. A formulation comprising:
>
> a vascular endothelial growth factor (VEGF) antagonist,
>
> an organic co-solvent,
>
> a buffer, and
>
> a stabilizing agent,
>
> wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and

wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.

Id. at 19:65–20:40. Claims 2–9 and 11–18 depend from claims 1 and 10, either directly or indirectly.

E. The Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–18 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §[1]	Reference(s)/Basis
1	1–18	102	Fraser[2]
2	1–18	103	Fraser, Wulff[3], Holash[4], '319 Publication[5], '309 Publication[6], McNally

[1] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112–29, 125 Stat. 284 (2011), amended 35 U.S.C. § 103, was effective on March 16, 2013. Because the '992 patent claims priority to a provisional application that has a filing date before March 16, 2013, and Petitioner does not currently contest this priority date, we apply the pre-AIA version of § 103. We note that our analysis in this Decision would not change under AIA law.
[2] Fraser, Hamish M. 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*, J. Clin. Endocrinology & Metabolism, Vol. 90, No. 2, 1114–1122 (2005) (Ex. 1009, "Fraser").
[3] Wulff, Christine et al., *Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2*, Endocrinology, Vol. 143, No. 7, 2797–2807 (2002) (Ex. 1016, "Wulff").
[4] Holash, Jocelyn et al., *VEGF-Trap: A VEGF blocker with potent antitumor effects*, PNAS, Vol. 99, No. 17, 11393–11398 (2002) (Ex. 1010, "Holash").
[5] Papadopoulos et al., WO 00/75319 A1, published Dec. 14, 2000 (Ex. 1029, "the '319 publication").
[6] Kandel et al., US 2004/0265309 A1, published Dec. 30, 2004 (Ex. 1027, "the '309 publication").

Ground	Claim(s) Challenged	35 U.S.C. §[1]	Reference(s)/Basis
			2000[7], FDA Guidance[8]

Pet. 41. Petitioner submits the Declaration of Ralph Tarantino, R.Ph., Ph.D. (Ex. 1002) in support of institution of *inter partes* review. Patent Owner submits the Declarations of Alexander M. Klibanov, Ph.D. (Ex. 2001) and David M. Brown, M.D. (Ex. 2004).

F. Asserted Prior Art

1. Fraser (Ex. 1009)

Fraser, titled "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function," describes a study that evaluated "a potent, receptor-based VEGF antagonist, the VEGF trap." Ex. 1009, 1114. Specifically, Fraser describes administering VEGF $Trap_{R1R2}$, "a recombinant, chimeric protein comprising Ig domain 2 of human VEGF-R1 and Ig domain 3 of human VEGF-R2, expressed in sequence with the human [fragment crystallizable (Fc) region]." *Id.* at 1115. According to Fraser, "[c]ompared with earlier versions of receptor-based fusion proteins, the VEGF $Trap_{R1R2}$ exhibits greater affinity for VEGF-A (affinity constant—1 pM) as well as improved bioavailability and pharmacokinetic properties." *Id.* (citing Holash, Ex. 1010).

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[7] Paul McGoff & David S. Scher, *Solution Formulation of Proteins/Peptides* in PROTEIN FORMULATION AND DELIVERY vol. 99, 139–58 (Eugene J. McNally ed., 2000) (Ex. 1013, "McNally 2000").

[8] Food & Drug Administration, *Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999) (Ex. 1038, "FDA Guidance").

Fraser further describes a formulation in which "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mm phosphate, 5 mm citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." Ex. 1009, 1115. "The compounds were stored at -20 C until required, at which time they were thawed. Any compound remaining was stored at 4 C and used within 2 wk." *Id.*

2. Dix (Ex. 1021)[9]

Dix, titled "VEGF Antagonist Formulations," describes a stable liquid formulation including a VEGF-specific fusion protein antagonist. Ex. 1021, codes (54), (57). Dix refers to the antagonist as a "VEGF 'trap'" that comprises "a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component." *Id.* at 1:43–54. Dix provides several examples of formulations including VEGF trap (SEQ ID NO: 4). *See id.* at 7:7–12:20. In one embodiment, the formulation contains "about 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 25 mg/ml VEGF trap protein." *Id.* at 11:15–20. The formulation is characterized by a pH ranging from 6.0–6.1. *Id.* Stability testing over 36 months at 5° C provided the following results:

[9] Dix et al., US 8,110,546 B2, issued Feb. 7, 2012 (Ex. 1021, "Dix"). Petitioner relies on Dix as evidence "that the claimed level of stability is the natural result of the ingredients in the *Fraser* formulation." *See* Pet. 47.

TABLE 9

Stability and Activity of Liquid Formulation (VGT-FS405)

Months	% Native Configuration	Bioassay	Binding Assay	Protein Content mg/ml
0	99.7	106	72	25.0
1	99.9	119	4.4 pM*	25.2
2	99.6	102	5.4 pM*	25.1
3	99.6	97	88	25.1
6	99.6	101	106	25.0
9	99.4	89	126	25.4
12	99.5	85	95	25.2
18	99.4	99	81	25.5
24	99.3	75	95	25.6
36	98.8	109	79	25.6

Id. at 12:5–20.

3. Wulff (Ex. 1016)

Wulff, titled "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2," describes a study that evaluated the anti-angiogenic properties of VEGF Trap R1R2. Ex. 1016, 2797. Wulff describes "VEGF Trap R1R2 used in these experiments [as] a recombinant chimeric protein comprising portions of the extracellular, ligand binding domains of the human VEGF receptors Flt-1 (VEGF-R1, Ig domain 2) and KDR (VEGF-R2, Ig domain 3) expressed in sequence with the Fc portion of human [immunoglobulin G (IgG)]." *Id.* at 2798, Fig. 1.

Figure 1 is reproduced below:

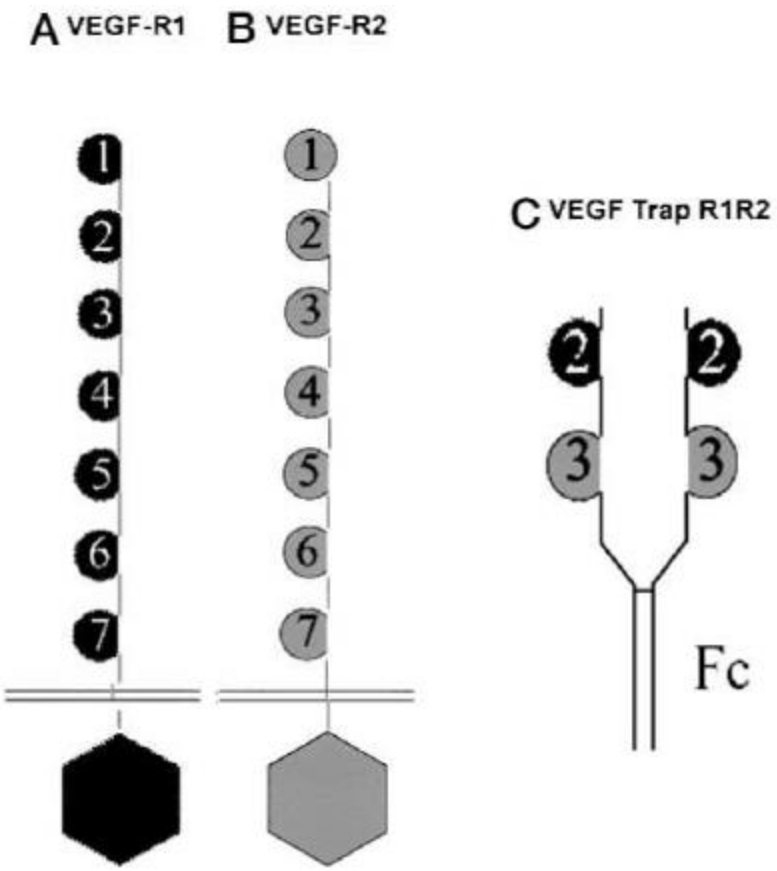

Figure 1A and 1B illustrates VEGF receptors R1 and R2, respectively. Ex. 1016, 2798. VEGF-R1 and VEGF-R2 are each illustrated as a line extending from an intracellular domain (filled hexagon), across a cell membrane (double-line), to seven extracellular domains individually illustrated as numbered circles on the line. *See id.* "These extracellular domains are responsible for VEGF binding." *Id.* Figure 1C illustrates VEGF Trap R1R2 as including the Fc portion of IgG with two extending arms, each including domain 2 of VEGF-R1 and domain 3 of VEGF-R2 shown as circles numbered 2 and 3, respectively. *See id.*

Wulff discloses that "[t]he presence of the Fc domain results in homodimerization of the recombinant protein, thereby creating a high affinity (KD1-5pM) VEGF Trap." Ex. 1016, 2798. Wulff further discloses that "the detailed molecular structure" of the VEGF Trap is described in the

PCT Publication WO 00/75319 A1 (the '319 application) (Ex. 1029). *Id.* at 2798 n.1. Additionally, according to Wulff, "[t]he VEGF trap was expressed in CHO cells and was purified by protein A affinity chromatography followed by size-exclusion chromatography." *Id.* at 2798.

4. Holash (Ex. 1010)

Holash is titled "VEGF-Trap: A VEGF blocker with potent antitumor effects." Ex. 1010, 11393. Holash describes engineering VEGF Traps. *Id.* Specifically, Holash describes the following process:

> The parental VEGF-Trap was created by fusing the first three Ig domains of $VEGF_{R1}$ to the constant region (Fc) of human IgG1. $VEGF\text{-}Trap_{\Delta B1}$ was created by removing a highly basic 10-aa stretch from the third Ig domain of the parental VEGF-Trap. $VEGF\text{-}Trap_{\Delta B2}$, was created by removing the entire first Ig domain from $VEGF\text{-}Trap_{\Delta B1}$. $VEGF\text{-}Trap_{R1R2}$ was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of these VEGF-Trap variants were produced and purified from Chinese hamster ovary cells.

Id. at 11393–11394.

5. The '309 publication (Ex. 1027)

The '309 publication, titled "Method of Tumor Regression with VEGF Inhibitors," relates to methods of administering a VEGF blocker to reduce tumor size and inhibit tumor metastases. Ex. 1027, codes (54), (57). The '309 publication states that, in a "preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF $trap_{R1R2}$) having the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQ ID NO: 2." *Id.* ¶¶ 5, 22. It also states, "[f]or a complete description of VEGF-receptor based antagonists including VEGFRIR2- FcΔC1(a), see PCT publication WO/00/75319, the contents of which is herein incorporated by reference in its entirety." *Id.* ¶ 22.

6. The '319 publication (Ex. 1029)

The '319 publication, titled "Modified Chimeric Polypeptides with Improved Pharmacokinetic Properties," relates to VEGF antagonists. Ex. 1029, code (54), 10:3–14. More specifically, the '319 publication describes VEGF antagonists including a VEGF receptor component linked to a multimerizing component. *Id.* at 10:3–14. The VEGF receptor component includes Ig domain 2 of the extracellular domain of a first VEGF receptor and Ig domain 3 of the extracellular domain of a second VEGF receptor. *Id.* The '319 publication further describes a host-vector system for producing the fusion polypeptide, wherein a CHO cell is the host cell. *Id.* at 12:19–26.

7. McNally 2000 (Ex. 1013)

McNally 2000 is titled "Solution Formulation of Proteins/Peptides." Ex. 1013, 139. McNally 2000 explains that "[t]he simplest and most economical way to formulate a protein is to develop a solution formulation." *Id.* According to McNally, a formulation scientist can determine whether a solution formulation will be acceptable for a given protein. *Id.* The scientist can use initial formulation studies to identify problems such as poor solubility or aggregation. *See id.* "For example, a particular pH or mix of buffer components used during processing may reduce solubility or induce aggregation." *Id.* at 139–140.

McNally 2000 further describes analytical test procedures for characterizing the physicochemical properties of the protein. Ex. 1013, 140. Typical properties monitored include conformation and size using size exclusion chromatography (SEC). *Id.*

McNally provides a "step-by-step[] how-to protocol" for a protein solution formulation development study. Ex. 1013, 156–157. "Ideally, the

protein concentration and solubility are determined first to establish a working range for the initial pH stability study." *Id.* at 156. "The next phase of experiments should focus on a narrower pH and concentration range and should study higher temperatures, possibly adding stabilizing excipients and extending the time frame of the study to at least one year. *Id.* at 157. "Specific buffer ion effects could be investigated during this phase." *Id.*

8. FDA Guidance (Ex. 1038)

FDA Guidance is titled "Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics." Ex. 1038. The Guidance provides general principles for submitting information on packaging materials used for human drugs and biologics. *Id.* at 1. The FDA Guidance explains that "[i]njectable dosage forms represent one of the highest risk drug products" because "[a]ny contaminants present . . . can be rapidly and completely introduced into the patient's general circulation. *Id.* at 23–24. Injectable products, whether small-volume or large-volume parenterals, may be packaged in vials. *Id.*

III. DENIAL UNDER 35 U.S.C. § 325(d)

Patent Owner asserts that we should deny the Petition under 35 U.S.C. § 325(d) because the Petition presents substantially the same art and arguments that the Office previously analyzed and fails to show that the Office erred during prosecution. *See* Prelim. Resp. 58–68.

We have discretion to deny review when "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d) ("Section 325(d)"). In that respect, Section 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the

Office.[10] *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020) (precedential) ("*Advanced Bionics*").

In evaluating the exercise of discretion to deny institution under Section 325(d), the Board uses the following two-part framework: (1) determining whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of the first part of the framework is satisfied, determining whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics*, Paper 6 at 8.

In applying the two-part framework, we consider several non-exclusive factors, including:

> (a) the similarities and material differences between the asserted art and the prior art involved during examination;
>
> (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
>
> (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
>
> (d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art or patent owner distinguishes the prior art;
>
> (e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and
>
> (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.

[10] The Board institutes trial on behalf of the Director. 37 C.F.R. § 42.4(a).

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) ("*Becton, Dickinson*").

Factors (a), (b), and (d) relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics*, Paper 6 at 10. Factors (c), (e), and (f) "relate to whether the petitioner has demonstrated a material error by the Office" in its prior consideration of that art or arguments. *Id.* Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated a material error by the Office. *Id.*

A. The '992 Patent Prosecution History

The original application for the '992 patent was filed with a preliminary amendment cancelling claims 1–11 and listing new claims 12–29. Ex. 1004, 2–4.[11] Claims 12 and 21 were identical to now-issued claims 1 and 10, except that they lacked the last clause of the claims reciting the presence of at least 98% of the VEGF antagonist in native conformation following storage. *See id.*

In a Non-Final Action dated April 2, 2019, the Examiner rejected claims 12–29 for nonstatutory double patenting. Ex. 1004, 74–79. Specifically, the Examiner rejected claims 12–29 as being unpatentable over claims 1–7 and 11–17 of U.S. Patent No. 8,092,803 ("the '803 patent"), claims of other related patents, and claims 12–26 of co-pending Application No. 15/879,294. *See id.* at 77–79.

[11] The cited page numbers in Exhibit 1004 refer to the page numbers added by Petitioner in the bottom-right corner of the page.

In response, the applicant amended pending claims 12 and 21 to recite the native conformation limitation recited by now-issued claims 1 and 10, respectively. Ex. 1004, 90–91. The applicant filed a terminal disclaimer as to the '803 patent. *See id.* at 93, 96. The applicant argued that the amended claims were patentably distinct from the other patents and application asserted in the double-patenting rejection. *See id.* at 93–94. Specifically, the applicant argued that "[i]ndependent claims 12 and 21 have been amended to include an element relating to the stability of the protein conformation in storage over a period of time. This element is not contained within any of the claims" asserted by the Examiner in the double-patenting rejection, excluding the '803 patent. *Id.* Following the amendment and terminal disclaimer, the Examiner allowed the claims. *Id.* at 104–111.

B. Same or Substantially the Same Art or Arguments Previously Presented to the Office

We first consider whether Petitioner asserts the same or substantially the same art or arguments that previously were presented to the Office. *Advanced Bionics*, Paper 6 at 8. Patent Owner contends that "Petitioner's primary reference for both Grounds 1 and 2, Fraser (Ex.1009), was cited in an [Information Disclosure Statement ('IDS')] during prosecution of the application that resulted in the '992 patent. The Examiner signed the IDS as considered and thus is presumed to have considered it." Prelim. Resp. 53 (citing *Husky Injection Molding Systems, Ltd., et al., v. Plastipak Packaging, Inc.*, IPR2020-00428, Paper 24 at 11 (PTAB July 28, 2020)). Patent Owner also contends that Holash was presented to the Patent Office because "Holash (Ex.1010) is expressly cited in the specification of the '992 patent and incorporated by reference in its entirety." *Id.* at 54 (citing Ex. 1001, 1:50–52).

Patent Owner further argues that we should find Petitioner's additional references to be substantially the same as art that was presented to the Office. *See* Prelim. Resp. 54–60. First, Patent Owner contends that WO 2006/104852 (Ex. 2022) and U.S. Patent Publication No. 2006/0217311 (Ex. 2023), which were provided to the Examiner during prosecution, include the same data as in the Dix patent on which Petitioner relies. *Id.* at 54–56 (citing Ex. 1001, code (56); Ex. 1004, 87; Ex. 2022; Ex. 2023). Patent Owner also contends that Wulff is cumulative to Fraser (disclosing "the effects of a VEGF antagonist on the reproductive system of primates") and Holash (disclosing "using CHO cells to produce the VEGF antagonist"). *See id.* at 56–57.

Additionally, Patent Owner contends that "both Wulff (Ex.1016) and the '319 Publication (Ex.1029) were considered during prosecution of a continuation application filed by Patent Owner, Ex.2024; Ex.2025, which issued as U.S. Patent No. 11,066,458 ["the '458 patent"], Ex.2026." Prelim. Resp. 57. Patent Owner further contends that the relevant disclosures of the '309 Publication are cumulative of the '319 Publication, which was before the Patent Office during the prosecution of the '458 patent. *Id.* at 58.

Finally, Patent Owner contends that McNally 2000 and FDA Guidance "both simply describe general knowledge of the POSA." Prelim. Resp. 59. "Patent Owner does not dispute that these two references would have been part of the general knowledge of a POSA." *Id.*

Petitioner asserts that the "petition presents art and arguments that are materially different than those presented to the Office during prosecution of the '992 patent" and that the only rejections made during prosecution of the

application that led to the '992 patent were obviousness-type double-patenting rejections. Pet. 33.

Petitioner further argues that the prosecution of the prior applications in the patent family indicates that the Examiner did not consider the cited references. *See* Pet. 33–34. Specifically, Petitioner asserts that "[t]he prosecution histories of these applications do not contain any rejections over the prior art. Rather, the claims in the priority application were rejected only for obviousness-type double patenting, written description, and indefiniteness." *Id.* (citing Exs. 1039–1046). Petitioner contends that "reviewing the prosecution of all of the priority applications, in which no rejections over the prior art were made, but rather the claims were rejected for obviousness-type double patenting, it is apparent that the Examiner did not consider the *Fraser* reference." *Id.* at 34.

Finally, Petitioner argues that the Petition "raises new arguments about *Fraser* not before the Office during prosecution that are based on new evidence and prior art that were not before the Office during prosecution." Pet. 35. For example, Petitioner argues that "the *'319 Publication* or the *'309 Publication*, [disclose] that the VEGF $Trap_{R1R2}$ protein in the *Fraser* formulation is aflibercept." *Id.* Petitioner argues that Wulff discloses "that Regeneron's VEGF $Trap_{R1R2}$ protein was made using CHO cells." *Id.* And Petitioner argues that Dix discloses that "Patent Owner's own tests established that the *Fraser* formulation met (and indeed exceeded) the 99% native conformation limitation of the challenged claims." *Id.*

We agree with Patent Owner that Fraser was cited during prosecution of the application that led to the '992 patent and was, therefore, previously presented to the Office. *Advanced Bionics*, Paper 6 at 7–8 ("Previously presented art includes art made of record by the Examiner, and art provided

to the Office by an applicant, such as on an [IDS], in the prosecution history of the challenged patent."); Ex. 1004, 87. Because Fraser is Petitioner's sole reference for Ground 1, and primary reference for Ground 2, we, therefore, find that the same or substantially the same art was previously presented regardless of whether the other references are cumulative of ones that were presented during prosecution.

C. Whether the Office Erred in a Manner Material to Patentability

Because we find that the same or substantially the same art previously was presented to the Office, we turn to whether Petitioner demonstrates that the Office erred in a manner material to the patentability of the challenged claims. *Advanced Bionics*, Paper 6 at 8, 10; *see Becton, Dickinson*, Paper 8 at 24.

Petitioner contends that "through no fault of the examiner, the Office erred to any extent it evaluated *Fraser*." Pet. 36. Petitioner also argues that the petition "raises new arguments about *Fraser* not before the Office during prosecution that are based on new evidence" and explains how the Examiner erred in failing to apply Fraser against the claims. *Id.* at 35–36.

Patent Owner contends that Petitioner has not established error with respect to Fraser and that "Petitioner does not allege material error by the Patent Office with respect to any of [the] other key prior art, and there is none." Prelim. Resp. 62.

We find that Petitioner has sufficiently shown error in this case. As discussed further below with respect to the Grounds, the Petition establishes that the VEGF $Trap_{R1R2}$[12] protein disclosed in Fraser is the same as the one

[12] The term "VEGF $Trap_{R1R2}$" is denoted as "VEGF $Trap_{R1R2,}$" "VEGF$Trap_{R1R2}$" and "VEGF $trap_{R1R2}$" in the briefing and references. Petitioner also uses the term "aflibercept" interchangeably with these terms.

disclosed in the Dix publication. Petitioner has also shown that Fraser's VEGF $Trap_{R1R2}$ formulation is the same as that disclosed in Dix, which establishes that the Fraser formulation meets the 98% native conformation limitation of the challenged claims. We, therefore, find that the Petitioner demonstrates that the Examiner misapprehended or overlooked the teachings of Fraser in this regard, and we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d).

IV. ANALYSIS

A. Person of Ordinary Skill in the Art

"The level of skill in the art is a factual determination" that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that a person of ordinary skill in the art ("POSA") at the time of the invention "would have had a Ph.D. in pharmaceutical sciences or a similar field, with at least several years of experience in the development, manufacture and characterization of formulations of therapeutic proteins, including, for example, fusion proteins or antibodies." Pet. 30 (citing Ex. 1002 ¶¶ 39–43). Petitioner further asserts that the POSA "would have understood how to combine proteins with compatible excipients such as surfactants, stabilizers, salts and buffers of various pH values, and how to adjust these combinations in order to optimize their stability in liquid or solid form." *Id.* at 30–31. Petitioner asserts that the

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Because Fraser uses the term "VEGF $Trap_{R1R2}$" (Ex. 1009, 1115), we use the same nomenclature in this Decision.

POSA would have been able to assess stability and compatibility by using "state-of-the-art analytical methods, such as SEC." *Id.* at 31.

Patent Owner does not contest the characterization offered by Petitioner. *See* Prelim. Resp. 16.

For purposes of this Decision, we adopt Petitioner's characterization because it is consistent with the level of skill in the art at the time of the invention as reflected by the '992 patent and the cited prior art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))).

B. Claim Construction

We interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.100(b) (2019). Under this standard, we construe the claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.*

Petitioner proposes claim construction for three terms under their plain and ordinary meaning. *See* Pet. 41–42. First, Petitioner asserts that the "POSA would have understood that the term 'native' in the phrase 'native conformation' in claims 1, 2, 10 and 11 refers to the fully intact and functional conformation of the protein." *Id.* at 42 (citing Ex. 1002 ¶ 22). Second, Petitioner asserts that the "POSA would have understood the term 'vial' in claims 1–9 to refer to a small closed or closable vessel, especially for liquids." *Id.* (citing Ex. 1031; Ex. 1002 ¶¶ 23, 190). Third, Petitioner

asserts that the "[t]he POSA would have understood the term 'multimerizing component' in claims 1 and 10 to refer to a protein moiety that joins two or more protein domains together to form a multimer, such as a dimer or trimer." *Id.* (citing Ex. 1002 ¶ 24). Patent Owner does not challenge Petitioner's proposed claim constructions. Prelim. Resp. 16.

For purposes of this Decision, however, we determine that no claim terms require express construction. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.")).

C. Asserted Anticipation of Claims 1–18 by Fraser

Petitioner contends that claims 1–18 are anticipated by Fraser. Pet. 42–53. Patent Owner disputes Petitioner's contentions. Prelim. Resp. 16–44.

1. Principles of Law

To establish anticipation under 35 U.S.C. § 102, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008); *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). Each element of the challenged claim must be found, either expressly or inherently, in the single prior art reference. *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). When evaluating a prior art reference in the context of anticipation, the reference must be "considered together with the knowledge of one of ordinary skill in the pertinent art." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (citing *In re Samour*, 571 F.2d 559, 562 (CCPA

1978)). "[A] reference can anticipate a claim even if it 'd[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination." *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)).

2. Petitioner's Position

Petitioner contends that Fraser discloses a formulation comprising a VEGF antagonist, specifically VEGF $Trap_{R1R2}$. Pet. 43 (citing Ex. 1009, 1115; Ex. 1002 ¶ 90). According to Petitioner, VEGF $Trap_{R1R2}$ is a fusion protein comprising Ig domain 2 of VEGF-R1, Ig domain 3 of VEGF-R2, and human Fc, a multimerizing component. *Id.* (citing Ex. 1009, 1115). Petitioner contends that Fraser further discloses that the formulation includes an organic co-solvent, i.e., Tween 20 (polysorbate 20); buffer, i.e., phosphate, citrate, and NaCl (pH 6.0); and a stabilizing agent, i.e., glycerol or sucrose. *Id.* at 44–45 (citing Ex. 1009, 1115; Ex. 1002 ¶¶ 73, 91–92). As to claim 1 specifically, Petitioner contends that "[t]he *Fraser* formulation was necessarily present in a 'vial' and a POSA reading *Fraser* would have understood this." *Id.* at 48–50 (citing Ex. 1002 ¶¶ 104–113).

Petitioner notes that Fraser states that the VEGF $Trap_{R1R2}$ formulation contained either 20% glycerol or 20% sucrose, but cites to Regeneron's prosecution statements and lab notebooks as indicating that the Fraser formulation contained 20% sucrose. Pet. 45 (citing Ex. 1022, Exhibit C; Ex. 1023, 2). Petitioner also contends that a POSA would have understood that Fraser's VEGF $Trap_{R1R2}$ was produced in CHO cells. *Id.* Specifically, Petitioner contends that Fraser's VEGF $Trap_{R1R2}$ "'was provided' by Regeneron," and Fraser references Holash to describe the properties of

VEGF $Trap_{R1R2}$. *Id.* (citing Ex. 1009, 1115). According to Petitioner, Holash discloses that VEGF $Trap_{R1R2}$ was produced and purified from CHO cells. *Id.* (citing Ex. 1010, 11393–11394). Petitioner asserts that Fraser's reference to VEGF $Trap_{R1R2}$ being "provided" by Regeneron and the disclosure of Holash "would have informed a POSA that the VEGF$Trap_{R1R2}$ in *Fraser* was produced in CHO cells." *Id.* at 45–46 (citing Ex. 1002 ¶¶ 93–95). Similarly, Petitioner asserts that Wulff, the '319 publication, and the '309 publication also confirm that Fraser's VEGF $Trap_{R1R2}$ protein was produced in CHO cells. *See id.* at 46 (citing Ex. 1016, 2798; Ex. 1027 ¶ 26; Ex. 1029, Example 21; Ex. 1002 ¶¶ 93–95).

Petitioner acknowledges that Fraser does not disclose that at least 98% of VEGF $Trap_{R1R2}$ in the formulation is present in native conformation after storage at 5° C for two months. *See* Pet. 46. However, Petitioner argues that "the stability of the *Fraser* formulation is the natural result of its ingredients." *Id.* (citing Ex. 1002 ¶¶ 96–102). First, Petitioner contends that "[t]he fact that the *Fraser* formulation has the same ingredients as the claimed formulation is enough to establish a *prima facie* case of anticipation," *Id.* at 46–47 (citing *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977)). Second, Petitioner asserts that "[a]nother Regeneron publication, *Dix*, published after the priority date, disclosed that Regeneron conducted stability testing on the same formulation and found that greater than 99% of the aflibercept remained in native conformation as measured by SEC after storage for 2 months at 5 °C." *Id.* at 47–48 (citing Ex. 1002 ¶¶ 96–102; Ex. 1021, 11:15–12:20, Table 9; Ex. 1002 ¶¶ 97, 100).

3. Patent Owner's Position

Patent Owner raises two main arguments. First, Patent Owner contends that Petitioner has not shown that Fraser's formulation meets the

"native conformation limitation." *See* Prelim. Resp. 16–41. Second, Patent Owner contends that Petitioner has not shown that Fraser's fusion protein was created in CHO cells. *See id.* at 41–44.

Patent Owner's first argument seeks to distinguish Fraser's VEGF $Trap_{R1R2}$ from Dix's VEGF trap protein (amino acid SEQ ID NO:4), so that Petitioner cannot rely on Dix's stability data for inherency. *See* Prelim. Resp. 16–18; *see* Sur-Reply 1–3. Patent Owner argues that "Fraser and Wulff set forth the broad structural characteristics needed to qualify as a 'VEGF$Trap_{R1R2}$' or 'R1R2,' which is a genus of fusion proteins, not a single molecule." Prelim. Resp. 19 (citing Ex. 2001 ¶¶ 39–43). Patent Owner also argues that the '319 publication supports this contention by disclosing that two R1R2 fusion proteins, Flt1.D2.Flk1D3.FcΔC1(a) and VEGFR1R2-FcΔC1(a), "are distinct fusion proteins, with distinct amino acid sequences." *Id.* at 20–25 (citing Ex. 1029, 21:16–17, 22:1–2, 51:5–12, 58:22–59:10, 61:2–8, 67:4–15, Figures 21A–21C, 24A–24C; Ex. 2001 ¶¶ 46–50, 53–61, 63–65).

According to Patent Owner, for the same reasons, the '319 publication and the '309 publication do not establish "that Fraser or Wulff used 'VEGF-$Trap_{R1R2}$' or similar terms to refer to—and only to—aflibercept."[13] Prelim. Resp. 35–37; *see* Sur-Reply 5. Finally, Patent Owner argues that Petitioner cannot use Patent Owner's "post-priority statements" to show that Fraser's VEGF $Trap_{R1R2}$ is the same as Dix's protein. *See* Prelim. Resp. 32–35.

[13] In response to these arguments, Petitioner contends that the VEGF $Trap_{R1R2}$ protein, disclosed by Fraser, Wulff, and Holash, and VEGFR1R2-FcΔC1(a), disclosed by the '309 publication, all refer to the same protein, "aflibercept" and that Patent Owner has previously referred to VEGF $Trap_{R1R2}$, described in Holash, as aflibercept. *See* Reply 1–4; Pet. 14 n.1 (citing Ex. 1020, 2, 6–7; Ex. 1002 ¶ 64).

According to Patent Owner, their statement to the Office that "[t]he name of the active ingredient of EYLEA™ is aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP$_{R1R2}$," merely indicates that "aflibercept may sometimes be referred to by the name of the genus to which it belongs . . . ." *Id.* at 32–33. Patent Owner further argues, that as a matter of law, "Patent Owner's post-priority date statements cannot be relied upon to 'fill in' missing disclosures in the prior art." *Id.* at 34; *see* Sur-Reply 3–4 (citing *Endo Pharms. Sols., Inc. v. Custopharm, Inc.*, 894 F.3d 1374, 1383 (Fed. Cir. 2018) ("*Endo*")).

Separately from arguing that Fraser does not disclose the same fusion protein as Dix, Patent Owner also argues that neither Fraser nor Wulff discloses the same formulation as Dix. *See* Prelim. Resp. 37–41. Patent Owner contends that "Fraser does not make clear that it used '20% sucrose' as a stabilizer, as Dix did." *Id.* Thus, Patent Owner contends that one cannot assume "that the data disclosed in Dix applies to the formulation used in Fraser when Petitioner fails to show that both references used the same formulation." *Id.* Patent Owner further argues that Petitioner's expert concedes that Fraser's formulation and Dix's formulation have different lot numbers, "suggesting that the proteins and/or formulations are *not* the same." *Id.* at 28 (citing Ex. 1002 ¶ 101 n.6).

Patent Owner's second main argument is that Petitioner fails to demonstrate that Fraser's VEGF Trap$_{R1R2}$ was necessarily created in CHO cells. *See* Prelim. Resp. 41–44. Patent Owner argues that Fraser's reference to Holash does not indicate that the same VEGF Trap$_{R1R2}$ from Holash was used by Fraser or that Holash's host cell applies to Fraser but, rather, Holash is cited for other properties of VEGF Trap$_{R1R2}$. *See id.* at 41–43 (citing Pet. 45; Ex. 1009, 1115; Ex. 1017, 1393).

With regard to the disclosure of Wulff, Patent Owner argues that "[w]hether Wulff might cause a POSA to speculate that perhaps CHO cells were used to produce the Fraser protein is not relevant to whether Petitioner has shown that Fraser *anticipates* the challenged claims." Prelim. Resp. 43–44. Accordingly, Patent Owner contends that "Petitioner thus has not met its burden to show that Fraser discloses that the particular VEGF $Trap_{R1R2}$ protein used therein was produced in CHO cells." *Id.* at 44.

4. Analysis

We first address Patent Owner's argument that Petitioner has failed to show that Fraser discloses the same protein as in Dix (SEQ ID NO:4) because Dix refers to a specific protein while Fraser refers to a genus of proteins. Prelim. Resp. 18–37.

We agree with Petitioner that Fraser discloses VEGF $Trap_{R1R2}$ as a specific protein molecule, describing it as "a recombinant, chimeric *protein*" that is "*a successor molecule*" to Patent Owner's earlier $VEGTrap_{A40}$. Reply 1–2 (citing Ex. 1009, 1114–15). Fraser refers to the protein as "*the* VEGF $Trap_{R1R2}$" and reports its specific physical, pharmacokinetic, and pharmacodynamic properties. *Id.* at 2 (citing Ex. 1009, 1115). The '309 publication also indicates that VEGF $Trap_{R1R2}$ is a particular protein having a specific amino acid sequence. Ex. 1027 ¶ 5 ("In a specific and preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF $trap_{R1R2}$) having the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQ ID NO: 2").[14]

[14] Petitioner represents that the amino acid sequence from the '309 publication is the same as the one disclosed in Dix as well as other Regeneron publications. *See* Pet. 14–15, 24–25, 47–48 (citing Ex. 1002 ¶¶ 64, 65, 97; Ex. 1029, 12, 15, Fig. 24A–24C; Ex. 1028 ¶ 8. SEQ ID Nos. 3

We further agree with Petitioner that Wulff discloses "[t]he VEGF $Trap_{R1R2}$ used in [its] experiments" as a single protein with a specific structure. Reply 2 (citing Ex. 1016, 2798) (alterations in original). Wulff discloses that "VEGF $Trap_{R1R2}$" was a "new compound" and "a recombinant chimeric protein" and that the "detailed molecular structure" of the protein "and how it was created" was described in the '319 publication. Ex. 1016, 2797–98, 2798 n.1, 2804.

We are not persuaded by Patent Owner's argument that the '319 publication supports its assertion that the protein disclosed in Fraser is a genus of proteins because the '319 publication discloses that two R1R2 fusion proteins, Flt1.D2.Flk1D3.FcΔC1(a) and VEGFR1R2-FcΔC1(a), "are distinct fusion proteins, with distinct amino acid sequences." Prelim. Resp. 20–25. The '319 publication refers to these two proteins as two "R1R2" proteins, not as two "VEGF $Trap_{R1R2}$" proteins. Patent Owner does not cite to any references in which the term, "VEGF $Trap_{R1R2}$," is used to refer to more than one protein. Thus, we find that, on the current record, Petitioner has sufficiently shown that the VEGF $Trap_{R1R2}$ protein disclosed in Fraser is a specific protein having the same amino acid sequence as the protein disclosed in Dix.

We further find that Petitioner has shown that Fraser discloses the claimed formulation. On the current record, Petitioner sufficiently demonstrates that Fraser's VEGF $Trap_{R1R2}$ formulation includes an organic co-solvent, i.e., Tween 20 (polysorbate 20); buffer, i.e., phosphate, citrate,

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and 4; Ex. 1019, 10:15–17, Figs. 24A–24C; Ex. 1019, 10:15–17, Figs. 24A–24C; Ex. 1020, 6–7; Ex. 1021, 11:15–12:20, Table 9). Patent Owner does not contest this representation.

and NaCl (pH 6.0); and a stabilizing agent, i.e., glycerol or sucrose. Ex. 1009, 1115; Ex. 1002 ¶¶ 73, 91–92.

Patent Owner asserts that Petitioner has not shown that Fraser discloses the same formulation as Dix because "Fraser does not make clear that it used '20% sucrose' as a stabilizer, as Dix did." Prelim. Resp. 37–41. Fraser discloses that the formulation includes "either 20% glycerol or 20% sucrose." Ex. 1009, 1115. Petitioner cites to lab notebook pages and statements made by Patent Owner during patent prosecution to show that Fraser used 20% glucose in its formulation. *See* Pet. 45 (citing Ex. 1023, 2). Specifically, during prosecution of Dix, Patent Owner submitted lab notebook pages showing the "actual lot and formulation used in Fraser," which included "20% sucrose." Ex. 1023, 2 (citing Ex. 1022, Exhibit C). Petitioner also cites to Wulff, which discloses use of a VEGF $Trap_{R1R2}$ formulation including "20% (wt/vol) sucrose." Pet. 28 (citing Ex. 1016, 2798).

Although Patent Owner's statements during prosecution of Dix establish that the Fraser formulation did, in fact, include 20% sucrose, Patent Owner contends that the "post-priority date statements cannot be relied upon to 'fill in' missing disclosures in the prior art as a matter of law." Prelim. Resp. 34 (citing *Endo*, 894 F.3d at 1378–83). We find the *Endo* case to be distinguishable. In *Endo*, the claims required a benzyl benzoate co-solvent to be present in a particular ratio with the solvent and the prior art did not even disclose the use of a co-solvent in the formulation. *Endo*, 894 F.3d at 1380–1383. The court found that the prior art disclosure was insufficient to show inherency of the benzyl benzoate in the claimed ratio despite it being later revealed that it was used in the formulation because the prior art, "failed to disclose that the composition's vehicle formulation included

another, key ingredient, benzyl benzoate, let alone the ratio of benzyl benzoate to castor oil." *Id.* at 1383. The court also found that "there was no evidence in the record that a skilled artisan could determine the non-disclosed vehicle formulation based on the reported pharmacokinetic performance profile, or that the non-disclosed vehicle formulation was necessarily a feature of the TU injection studied in the [prior art]." *Id.* The court concluded that, "[u]nder the circumstances of this case, the incomplete description of the TU injection composition elements denied skilled artisans from having access to that composition, thereby precluding use of the inherency doctrine to fill in disclosure about the product missing from the [prior art]." *Id.*

In this case, Fraser discloses a VEGF $Trap_{R1R2}$ formulation that includes "either 20% glycerol or 20% sucrose." Ex. 1009, 1115. In other words, Fraser provides an option of including 20% of two different possible stabilizing agents, in contrast to the prior art in *Endo*, which did not even disclose the use of a co-solvent (and included no disclosure of any co-solvent amount). As such, we find that, on the current record, one of ordinary skill in the art would be able to "at once envisage" a VEGF $Trap_{R1R2}$ formulation with 20% sucrose. *See Kennametal*, 780 F.3d at 1381. As a result, the Fraser disclosure does not "den[y] skilled artisans from having access to that composition," as was the case in *Endo*.

Because we find, on the current record, that Petitioner has sufficiently shown that the VEGF $Trap_{R1R2}$ formulation in Fraser is the same as that in Dix, we also find that Petitioner can rely on Dix to show the stability of the protein. As argued by Petitioner, Dix shows that greater than 99% of VEGF $Trap_{R1R2}$ remained in native conformation as measured by SEC after storage for 2 months at 5° C. Ex. 1002 ¶¶ 96–102; Ex. 1021, 11:15–12:20, Table 9.

We agree with Petitioner that, while Fraser does not disclose this stability information, as evidenced by the data in Dix, such stability is necessarily a natural result of the formulation ingredients. Pet. 46 (citing *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 471 F.3d 1363, 1367 (Fed. Cir. 2006) (holding that "[o]ur cases have consistently held that a reference may anticipate even when the relevant properties of the thing disclosed were not appreciated at the time.").

We also find that Petitioner has sufficiently shown that Fraser discloses that the VEGF $Trap_{R1R2}$ disclosed therein was produced in CHO cells, as required by the claims. Fraser discloses that VEGF $Trap_{R1R2}$ "was provided" by Regeneron and cites to the Holash paper in discussing the properties of VEGF $Trap_{R1R2}$. Ex. 1009, 1115. The Holash paper (Reference 21 in Fraser) states that "[a]ll of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells." Ex. 1010, 11394.[15]

We acknowledge Patent Owner's argument that Fraser's citation to Holash does not mean that Fraser necessarily used CHO cells because Fraser does not "say that the VEGF $Trap_{R1R2}$ used by the Fraser authors is the same as any of the VEGF-Trap variants described in Holash" (Prelim. Resp. 41); however, on the current record, we are persuaded by the testimony of Dr. Tarantino that the "VEGF$Trap_{R1R2}$ disclosed in *Fraser* was created in CHO cells, and a POSA would have known as much when reading the term

[15] Wulff also discloses that VEGF $Trap_{R1R2}$ was manufactured in CHO cells and explains that the '319 publication describes "the detailed molecular structure" of VEGF $Trap_{R1R2}$ "and how it was created." Ex. 1016, 2798, 2798 n.1. The '319 publication (and the '309 publication) also confirm that VEGF $Trap_{R1R2}$ was produced in CHO cells. Ex. 1027 ¶ 22; Ex. 1029, Example 21; Ex. 1002 ¶¶ 93–95.

'VEGFTrap$_{R1R2}$' in the context of the whole *Fraser* article." Ex. 1002 ¶ 93. As discussed above, Fraser refers to a particular protein, VEGF Trap$_{R1R2}$, and cites to a Regeneron publication (Holash) as describing the properties of this protein. Ex. 1009, 1115. Fraser then states that VEGF Trap$_{R1R2}$ was provided by Regeneron to conduct the experiments described therein. *Id.* Based on this disclosure in Fraser, on the current record, we credit the currently unrebutted testimony of Dr. Tarantino that "[t]he reference by *Fraser* to VEGFTrap$_{R1R2}$ being "provided" by Regeneron and directing the reader to *Holash* for a description of the protein would have informed the POSA that the VEGFTrap$_{R1R2}$ in *Fraser* was made in CHO cells." Ex. 1002 ¶ 94.

Patent Owner does not contest that Fraser discloses the other limitations of claims 1 and 10 and, on the current record, we find that Fraser does disclose these limitations. Accordingly, on the current record, Petitioner has demonstrated a reasonable likelihood that the subject matter of claims 1 and 10 of the '992 patent is anticipated by the disclosure of Fraser. Petitioner also presents evidence and arguments as to how Fraser anticipates dependent claims 2–9 and 11–18. Pet. 48–53. Other than the arguments discussed above, Patent Owner does not present additional arguments further addressing the patentability of these claims. We have reviewed Petitioner's arguments and evidence regarding these claims and find that, on the current record, Petitioner has also demonstrated a reasonable likelihood that claims 2–9 and 11–18 of the '992 patent are anticipated by the disclosure of Fraser.

D. Asserted Obviousness over Fraser, Holash, and Wulff, in view of the '319 Publication, the '309 Publication, McNally 2000, and FDA Guidance

Petitioner contends that claims 1–18 would have been obvious over the combination of Fraser, Holash, and Wulff, in view of the '319 Publication, the '309 Publication, McNally 2000, and FDA Guidance. Pet. 53–67. Patent Owner disputes Petitioner's contentions. Prelim. Resp. 44–52.

1. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the subject matter sought to be patented and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) when in evidence, objective evidence of non-obviousness, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

2. Petitioner's Position

Petitioner argues that it would have been obvious for one of ordinary skill in the art to produce Fraser's VEGF $Trap_{R1R2}$ in CHO cells and formulate the resulting VEGF $Trap_{R1R2}$ into a stable formulation for therapeutic use having the claimed stability. *See* Pet. 54–63.

First, Petitioner contends that it would have been obvious to produce Fraser's VEGF $Trap_{R1R2}$ in CHO cells because Holash and Wulff describe

producing the same fusion protein in CHO cells. *See* Pet. 56 (citing Ex. 1016, 2798; Ex. 1010, 11393–11394). Petitioner asserts that a POSA would "stick[] to a proven method that was already shown to have worked." *Id.* at 56–57 (citing Ex. 1002 ¶¶ 143–145, 189; Ex. 1047, 12; Ex. 1017, 1396).

Second, Petitioner contends that it would have been obvious "to select an organic cosolvent, a buffer, and a stabilizing agent as excipients for a stable formulation" because "this was the *only* formulation of aflibercept that was published for *in vivo* use." Pet. 58 (citing Ex. 1009, 1115; Ex. 1016, 2798; Ex. 1002 ¶¶ 146–147). Petitioner asserts that Fraser teaches "this formulation sufficiently stabilized the aflibercept so that it remained useable over a two-week period when stored at 4º C." *Id.* at 58 (citing Ex. 1009, 1115).

Third, Petitioner argues that the native conformation limitation does not distinguish the claimed formulation from the prior art. *See* Pet. 59–63. Petitioner contends that "[m]erely claiming the results achieved by an obvious combination of ingredients does not distinguish that combination from the prior art." *Id.* at 59 (citing *In re Best*, 562 F.2d at 1255). Petitioner further argues that storage stability is not critical to the formulation and instead, "[t]his limitation appears to only be the product of simply claiming the test results reported in the examples of the '992 patent." *Id.* Petitioner further argues that "a POSA would have been motivated to use the *Fraser* formulation [to] make a commercial aflibercept product that was as stable as possible." *Id.* at 60. To do so, Petitioner argues that a POSA would have been motivated to minimize aggregation, because aggregates reduce the quality and potency of the product. *See id.* (citing Ex. 1002 ¶¶ 72–74, 154). Petitioner argues that "[a] POSA thus would have regarded the preservation

of at least 98% of the aflibercept in native conformation after storage for two months at 5º C as measured by SEC as being an obvious and desirable goal, and a level of 99% or greater to be even more desirable." *Id.* at 61 (citing Ex. 1002 ¶ 153).

Fourth, Petitioner argues that a POSA would have made a stable formulation —defined by the native conformation limitation—by "simply doing the obvious thing and copying the *Fraser* formulation." Pet. 61. Petitioner argues that "[a]s of 2006, formulators possessed a relatively high degree of skill in stabilizing protein therapeutics." *Id.* Accordingly, Petitioner argues that "a POSA would have been able to make incremental adjustments to the concentrations of polysorbate 20, phosphate buffer, aflibercept, NaCl and pH, observed their impact on stability, and then made additional adjustments as necessary until they achieved maximum stability." *Id.* (citing Ex. 1002 ¶¶ 153–159). Petitioner argues that McNally shows that it "would have been routine and well within ordinary skill" to design and execute experiments to determine the optimal value for each variable. *See id.* at 62 (citing Ex. 1002 ¶¶ 156–159; Ex. 1013, 156–157).

3. Patent Owner's Position

Patent Owner argues that Petitioner may not rely on inherency to demonstrate obviousness, and that Petitioner has not shown a motivation to modify the references nor a reasonable expectation of success in doing so. *See* Prelim. Resp. 45–52. First, Patent Owner argues that "Petitioner advances the same inherency argument for its obviousness ground that it did for its anticipation ground, attempting to rely on the non-prior art Dix reference." *Id.* at 46. However, Patent Owner argues that "[t]he data from Table 9 of Dix could not have informed the POSA's understanding of the

stability of the Fraser formulation by the critical date because it did not exist as of the critical date" *Id.*

Second, Patent Owner argues that it would not have been obvious to seek a 98% native conformation. *See* Prelim. Resp. 47–49. Patent Owner argues that "it is not the case that formulators *always* attempt to get as close to 100% native conformation as possible—only driven by hindsight would a formulator set aside other constraints and priorities and seek single-mindedly to maximize native conformation." *Id.* at 48 (citing Ex. 1006, 2, 4, 6; Ex. 2001 ¶¶ 25–27). According to Patent Owner, Petitioner's references "describe formulations as 'stable' when a much lower fraction of the product—between 90% and 95%—was present in native conformation." *Id.* (citing Ex. 1030, 8:31–33; Ex. 1026 ¶ 63; Ex. 1024 ¶ 36; Ex. 1025 ¶ 25). Patent Owner further argues that "native conformation below 98% was consistent with certain generally applicable standards." *Id.* at 49 (citing Ex. 2014, 14; Ex. 2021, 5).

Third, Patent Owner argues that "Petitioner has not shown that, based on information available as of the priority date, a POSA would have reasonably expected the formulation of Fraser to exhibit at least 98% native conformation under the recited conditions." Prelim. Resp. 50. Specifically, Patent Owner argues that Fraser's disclosure of storing the compound at 4° C for 2 weeks "does not imply that the formulation would have maintained at least 98% native conformation after two months, or anything close to it." *Id.* at 50 (citing Ex. 1009, 1115; Pet. 58). Notably, Patent Owner argues that usability at two weeks does not imply stability over two months as aggregates tend to form over time. *See id.* (citing Ex. 2020, 4; Ex. 1021, Examples 1–3). Finally, Patent Owner argues that "adequacy of a

formulation for a preclinical study does not imply adequacy for clinical trials and approval." *Id.* at 50–51 (citing Ex. 1013, 147; Ex. 1006, 10).

4. Analysis

For the reasons explained above, we find that, on the current record, Petitioner has shown that Fraser discloses the limitations of the challenged claims of the '992 patent. However, even, *assuming arguendo*, that Fraser does not disclose certain limitations, on the current record, we find that those limitations would have been obvious based on the disclosures in the other cited references. We are persuaded by Petitioner and Dr. Tarantino's contentions that the "prior art would have given a POSA ample motivation of making a formulation" with VEGF $Trap_{R1R2}$ based on studies published by Regeneron showing that VEGF $Trap_{R1R2}$ "had the best *in vivo* pharmacokinetics and anti-VEGF activity of the VEGF-trap proteins Regeneron had been studying." Pet. 55 (citing Ex. 1009; Ex. 1010; Ex. 1016; Ex. 1029, 10 (describing VEGF$Trap_{R1R2}$ as having "improved pharmacokinetic properties"); Ex. 1002 ¶¶ 140–142).

Petitioner has also persuasively shown that "[t]he prior art also would have motivated a POSA to select an organic cosolvent, a buffer, and a stabilizing agent as excipients for a stable formulation of aflibercept" because Regeneron's Fraser and Wulff publications disclosed "that it had formulated aflibercept for its *in vivo* studies using the organic co-solvent polysorbate 20, a buffer containing phosphate, and the stabilizing agent sucrose." Pet. 58 (citing Ex. 1009, 1115; Ex. 1016, 2798; Ex. 1002 ¶¶ 146–147). We are further persuaded by the contention of Petitioner and Dr. Tarantino that this was the only formulation of aflibercept that was published for *in vivo* use as of the priority date, "which would have left the

POSA with only one clear starting point when making a formulation for such use." *Id.* (citing Ex. 1002 ¶ 147).

We are similarly persuaded by Petitioner's contention that a POSA would have been motivated to make VEGF $Trap_{R1R2}$ in CHO cells because Regeneron's Wulff and Holash publications disclosed that they had done so and a POSA would have done the same in order to reproduce the desirable performance of VEGF $Trap_{R1R2}$ in those publications. Pet. 56 (citing Ex. 1002 ¶¶ 143–145, 189; Ex. 1010, 11393–11394; Ex. 1016, 2798; Ex. 1047, 12; Ex. 1017, 1396).

Patent Owner's main argument is that a person of ordinary skill in the art would not have been motivated to produce a VEGF $Trap_{R1R2}$ formulation in which 98% of the VEGF antagonist is present in native conformation following storage at 5º C for two months, nor would a POSA have had a reasonable expectation of success in doing so. Patent Owner also argues that Petitioner may not use Dix to demonstrate obviousness of the claimed stability requirements because they allege that Petitioner cannot rely on inherency in the context of its obviousness arguments. Prelim. Resp. 44–52. Patent Owner contends that *In re Best* is distinguishable because "Petitioner's inherency argument is mistaken in the context of its anticipation argument, and Petitioner does not make a parallel single-reference obviousness argument [as in *Best*]." *Id.* at 47 n.1. Patent Owner also contends that "no party in *Best* attempted to show inherency with non-prior art data." *Id.*

As explained above, based on the current record, we do not find Petitioner's inherency arguments in the context of its anticipation argument to be "mistaken." Also, while we invite the parties to further brief this issue, we are not persuaded that the reasoning in *In re Best* is limited to the context

of a single-reference obviousness argument as asserted by Patent Owner. We are similarly unpersuaded that *In re Best* does not apply to situations in which inherency is shown with non-prior art data.

On the current record, we find that Petitioner has persuasively shown that a person of ordinary skill in the art would have been able to achieve the claimed stability limitations by making the VEGF $Trap_{R1R2}$ formulation disclosed in Fraser and Wulff. On the current record, we also agree with Petitioner that, if needed, one of skill in the art would have been able to optimize the Fraser formulation in view of the other cited references in order to achieve the claimed stability. *See E.I. Dupont de Nemours v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (The fact that routine or trial-and-error experiments may be required to determine the optimum concentrations of ingredients in an otherwise old or obvious formulation does not make the optimized formulation inventive).

Thus, after carefully considering the arguments and evidence, we determine that, on this record, Petitioner has demonstrated a reasonable likelihood that the subject matter of claims 1 and 10 of the '992 patent would have been obvious over the disclosures of Fraser, Holash, and Wulff, in view of the '319 Publication, the '309 Publication, McNally 2000, and FDA Guidance. Petitioner also presents evidence and arguments as to how these references render obvious dependent claims 2–9 and 11–18 of the '992 patent. Pet. 63–66. Other than the arguments discussed above, Patent Owner does not present additional arguments further addressing the patentability of these claims. We have reviewed Petitioner's arguments and evidence regarding these claims and find that, on the current record, Petitioner has demonstrated a reasonable likelihood that the subject matter of claims 2–9 and 11–18 of the '992 patent is rendered obvious by the

disclosure of Fraser, Holash, and Wulff, in view of the '319 Publication, the '309 Publication, McNally 2000, and FDA Guidance.

V. CONCLUSION

For the forgoing reasons, Petitioner has demonstrated a reasonable likelihood that at least one challenged claim of the '992 patent is anticipated by and/or would have been obvious over the prior art of record. Accordingly, we institute an *inter partes* review on claims 1–18 for all grounds set forth in the Petition.

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314, an *inter partes* review is instituted on claims 1–18 for all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, *inter partes* review of the '992 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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