

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.
Patent Owner.

Patent No. 10,464,992

Inter Partes Review No. IPR2023-00462

PATENT OWNER'S PRELIMINARY RESPONSE

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Statutes

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I. INTRODUCTION

Each challenged claim of U.S. Patent No. 10,464,992 (the “’992 patent”) requires a stability-related property: at a minimum, that “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.” Celltrion admits that this stability endpoint cannot be found in the prior art, and its attempt to link stability data from a reference that is not prior art to a prior art formulation is improper and misplaced. Indeed, even if the data from this reference were considered, the Petition fails to demonstrate it relates to the same protein present in the prior art formulation.

More specifically, in Petitioner’s anticipation and obviousness grounds, Petitioner relies on prior art that refers to “VEGF Trap,” “VEGF Trap R1R2,” or just “R1R2” proteins, all of which generally refer to *multiple, different* fusion proteins. But none of Petitioner’s prior art references include the detail necessary to confirm that they pertain to the same VEGF protein described in the non-prior art publications on which Petitioner relies for stability data. The lack of a specific link is significant because minor variations in the amino acid sequence of a protein can have outsized effects on a protein’s stability. Ex.2001 ¶¶ 63-68. Thus, even if one formulation of one VEGF Trap R1R2 protein may satisfy the claimed stability criteria, other formulations of others may not.

In this regard, Petitioner’s arguments parallel those that were raised, and rejected, by the Board in *Amgen, Inc. v. Alexion Pharms.*, IPR2019-00741, 2019 WL 4132685, at *9 (P.T.A.B. Aug. 30, 2019). In that proceeding, the prior art “refer[red] to a class or category” of proteins, at least one of which did not meet the claim requirements. The Board therefore concluded that the doctrine of inherency could not fill the gaps in the prior art. *Id.* at *9-*11. The same is true here.

Petitioner maintains that, even if the stability requirements of the claims are not inherent in the prior art, they would be obvious based on the combined teachings of seven different references and after adjusting the formulation further to maximize its stability. Pet. 58–62. But Petitioner’s argument is contradicted by the prior art on which it relies. As Petitioner’s references explain, a formulator balances competing objectives, rather than purely maximizing stability, and deals with challenges specific to each protein—because again, even small variations in a protein’s amino acid sequence can affect stability. Taken as a whole, the prior art does not support Petitioner’s assertions.

Petitioner’s failure to show invalidity is unsurprising given that the Petition is premised on art that is the same or substantially the same as art previously considered by the Patent Office. Thus, discretionary denial under 35 U.S.C. § 325(d) is also appropriate. The primary reference Petitioner relies on for

Grounds 1 and 2, Fraser (Ex.1009), is cited on the face of the '992 patent, but Petitioner asserts that “it is apparent that the Examiner did not consider the *Fraser* reference,” because no rejections over the prior art were made. Pet. 34. This assertion—that cited art is only relevant to § 325(d) if it forms the basis for a rejection during prosecution—is contrary to Board precedent. Petitioner then asserts that “through no fault of the examiner, the Office erred to any extent it evaluated *Fraser*.” Pet. 36. No explanation is given of how the Office erred, and therefore, Petitioner has failed to carry its burden to demonstrate material error with respect to Fraser. *Boehringer Ingelheim Animal Health USA Inc. v. Kansas State Univ. Rsch. Found.*, PGR2022-00021, 2022 WL 2784777, at *7 (P.T.A.B. July 15, 2022). The fact that the Examiner disagreed with Petitioner’s view of the prior art is not evidence of material error. Petitioner’s arguments with respect to the additional secondary references it relies on in the Petition fare no better. For at least these reasons, the Petition does not demonstrate a reasonable likelihood that any claim of the '992 patent is invalid.

II. BACKGROUND

A. Fusion Proteins, Antibodies, and EYLEA®

Vascular endothelial growth factor (“VEGF”) is a protein that regulates angiogenesis, or the growth of blood vessels. Ex.1002, ¶ 54; *see generally* Ex.2001 ¶ 17. In many cancers, VEGF enables the development of new blood

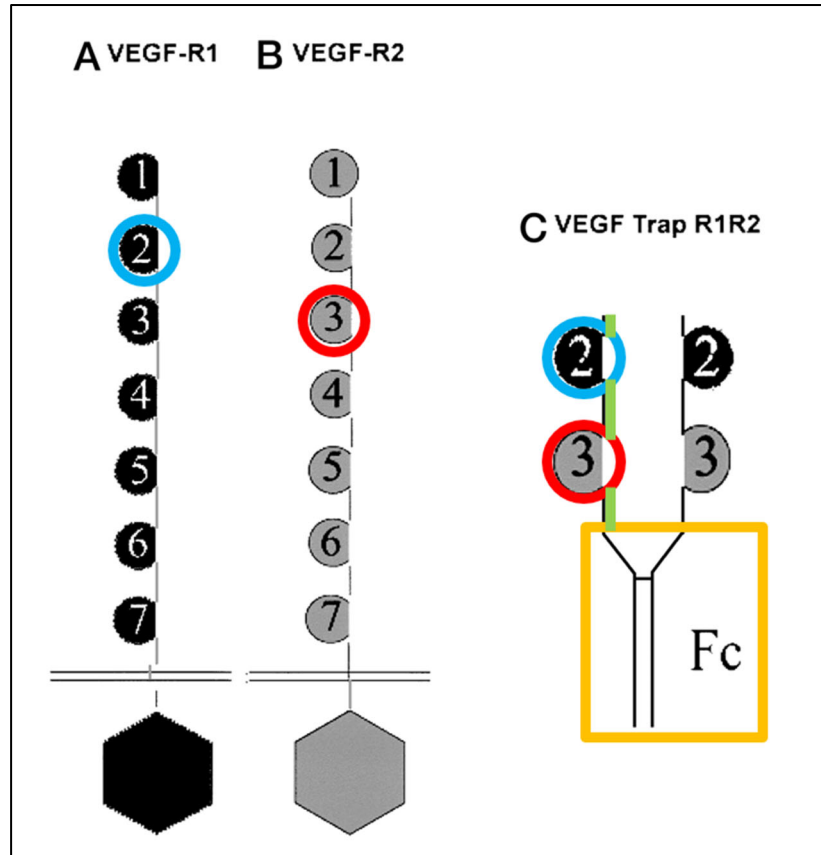
vessels in a growing tumor. Ex.1008, 967; Ex.1010, 11393. In 2004, the FDA approved the first VEGF antagonist for the treatment of cancer, an antibody called bevacizumab, or Avastin®. Ex.1008, 971; Ex.2003, 1.

The potential for VEGF antagonists in the treatment of angiogenic eye disorders was also recognized by this point in time. Ex.2004 ¶ 27. Angiogenic eye disorders, such as neovascular age-related macular degeneration (“wet AMD”), are characterized by pathologic growth of abnormal blood vessels and vascular leakage from damaged blood vessels in the retina. *Id.* ¶ 26. Macugen® (pegaptanib), a modified oligonucleotide, was approved after Avastin® in 2004, Ex.2006, 4; Ex.2007, 1, and was the first VEGF antagonist approved for treatment of angiogenic eye disorders. Ex.2004 ¶ 30; Ex.2005, 1, 6. In 2006, FDA also approved Lucentis® (ranibizumab), an anti-VEGF antibody fragment, for wet AMD. Ex.2004 ¶ 40; Ex.2008, 1, 4.

Although antibody drugs and processes for developing them were known by 2006, *see* Ex.2009, 3, Regeneron took a fundamentally different approach to developing a VEGF antagonist. Over the course of many years, Regeneron developed and tested novel anti-VEGF fusion proteins composed from VEGF receptor domain sequences, which could catch, hold, and block (“trap”) circulating VEGF. *See* Ex.2010, 1; *see generally* Ex.2001 ¶¶ 19-20. Regeneron investigated VEGF Trap proteins for multiple indications, initially in cancer and later in

angiogenic eye disorders. Ex.2011; Ex.1010; *see also* Ex.1009. Regeneron published its first phase I trial results, involving intravenous administration of a VEGF Trap to treat angiogenic eye disorders, no earlier than July 28, in 2006. Ex.2011. In 2011, Regeneron obtained FDA approval for aflibercept, a VEGF Trap protein, for the treatment of wet AMD. Ex.2012, 1; Ex.2001 ¶ 20.

“VEGF Traps” are a class of fusion proteins that include VEGF-binding domains of human VEGF receptors. *See* Ex.2013 ¶ 9; Ex.1010, 11393. The proteins may also include additional components, such as the Fc region of an antibody. *See* Ex.2013 ¶¶ 7, 63. In some publications, VEGF Traps are defined more specifically, based on the VEGF receptors from which the VEGF-binding domain sequences were derived. For example, “VEGF Trap R1R2” or “R1R2” denotes fusion proteins comprising portions of the extracellular, ligand binding domains from VEGF receptor 1, also known as “R1” (or as “Flt1”) and VEGF receptor 2, also known as “R2” (or as “Flk1” or “KDR”). Ex.1016, 2798; Ex.1009, 1115; Ex.1029, 58:22-59:10. Regeneron also experimented with VEGF Trap R1R3 proteins. Ex.1029, 58:22-59:10. The figure below shows an example of the domains used for one VEGF Trap R1R2 protein, with a selected binding domain from VEGFR1 (blue), a selected binding domain from VEGFR2 (red), and an Fc region of an antibody (gold):



Ex.1016, 2798 (annotations added). However, as indicated by the lines (green) between the domains, the fusion proteins, unlike antibodies, also feature non-natural bridging sequences that do not form a part of any of the domains.

Ex.2001 ¶ 21. Regeneron used the “R1R2” nomenclature to refer to proteins with these domains, even though the proteins have different bridging sequences.

Ex.1029, 1:14-16, 67:7-17; Ex.1010, 11393; Ex.2001 ¶¶ 44-61. Aflibercept is one of these VEGF Trap proteins, and it comprises bridging sequences in addition to a human antibody constant region and specific portions of the extracellular domains of VEGFR1 and VEGFR2. Ex.2001 ¶¶ 20-21.

Components of some of Regeneron's "VEGF Trap" proteins have structural overlap with monoclonal antibodies such as bevacizumab because the VEGF Trap proteins may include an "Fc" or "fragment crystallizable" region of an antibody. Ex.2013 ¶ 36; Ex.1010, 11393; *see generally* Ex.1011, 96. An Fc region generally contains the same constant regions across antibodies in the same class (e.g., IgG₁ antibodies) and does not confer binding specificity; in an antibody, binding specificity usually comes from the variable regions of the antibody. Ex.1011, 94-96. VEGF Trap proteins do not have variable regions. *See* Ex.2013 [0005]-[0009]; Ex.1010, 11393-11394. Instead, their binding specificity is determined by extracellular portions of VEGF receptors.

B. Stability of Biologic Drugs

Formulation of any protein presents a unique challenge to the formulator. The process involves competing priorities and constraints outside the formulator's control, such as the required dose, the route of delivery, the need for a multidose formulation suitable for dose titration or dose combination, and more. Ex.1006, 2, 4; Ex.2001 ¶¶ 25-27. The formulator must develop a formulation within these constraints, while at the same time achieving the required stability for an adequate shelf life. *See* Ex.2014, 12-13 (describing the relationship between proposed shelf-life and required stability studies). What constitutes a sufficiently stable formulation is product specific. Ex.1047, 5-6 ("Individual and/or collective

acceptance criteria for product-related substances should be set, as appropriate.”); Ex.2001 ¶ 27.

Proteins are subject to different types of chemical and physical degradation pathways. Ex.1001, 5:35-44; Ex.2015, 33-34; Ex.2001 ¶¶ 22-23. One common way in which proteins degrade is through aggregation. Aggregation generally occurs when proteins unfold to some degree and clump together as a result of attractions or bonds between the individual proteins or protein fragments. Ex.2001 ¶ 23; Ex.2015, 62-64; Ex.1047, 21.

Factors affecting aggregation vary based on the protein itself and its interactions with excipients in the environment. “The unfolding is primarily caused by the solvent environment (pH, salt, co-solvents, etc.), temperature, or surface interactions,” while the “initial stages of aggregation are quite specific in the sense that they involve the interaction of specific structural subunits of one molecule with ‘matching’ hydrophobic surface areas of structural subunits of a neighboring molecule.” Ex.2015, 63-64; Ex.2001 ¶ 24. As the prior art indicates, “[e]very protein has unique physicochemical characteristics and the potential to behave differently stability-wise.” Ex.1013, 145; Ex.2001 ¶ 24. Changes of even a few amino acids can affect protein stability under high and low temperatures. Ex.2001 ¶¶ 22, 63-68. And unlike naturally occurring proteins like antibodies, whose structure has evolved over millennia to achieve stabilizing interactions

between their various domains, fusion proteins lack such stabilizing forces and thus may be prone to sources of instability, including aggregation. Ex.2016, 12 (contrasting interdomain stability of native antibodies to fusion proteins, which “lack such stabilizing interdomain stabilization”); Ex.2017, 44 (“Aggregated product is often of concern with immunoadhesins [fusion proteins], since these proteins are nonnatural and so it is difficult to predict their solution behavior.”).

Depending on the drug, a formulator’s various other requirements may be in tension with the desire to achieve a formulation that is stable over a long shelf life. For example, the route of administration may constrain the dose volume.

Intravitreal administration involves injections into a small space in the back of the eye called the vitreous cavity, and as a result, a dose cannot practically exceed a certain maximum volume. Ex.2001 ¶ 25; *compare* Ex.1013, 141 (upper limit of 10-20 mL for IV administration); *with* Ex.2018 (finding elevated intraocular pressure with a dose volume of 0.05 mL). However, assuming the POSA wished to consider using a higher protein concentration in view of such dosing constraints (if a greater amount of protein were deemed necessary), the higher concentration would be expected to result in a lower shelf life because higher protein concentration generally leads to more aggregation. Ex.2001 ¶ 25; Ex.1002 ¶ 102 (“formulations with lower protein concentrations tend to exhibit *less* aggregation

than ones with higher concentrations.”) (citing Ex.1006, Table 6); *see* Ex.1013, 146 (“rates of degradation typically vary as a function of protein concentration.”).

As another example, if a multidose formulation is required, use of a preservative to prevent microbial contamination is typically necessary. Ex.1006, 10. But the use of preservatives can adversely affect the stability of a formulation, because “[i]n general, the addition of preservative(s), regardless of the preservative used, significantly changes the stability profiles of proteins” and can cause increased aggregation. *Id.*; Ex.2001 ¶ 26.

Ultimately, regardless of the formulation, some degradation will occur. “For most proteins, including relatively stable ones, at least some degradation should be expected even during refrigerated storage.” Ex.1006, 9. Characteristics of the protein itself may limit the available formulation approaches and maximum stability that may be achieved. Ex.1006, 14 (“Some problems related to the intrinsic properties of a protein cannot be overcome unless a change in the sequence is introduced.”); Ex.1013, 139 (“Lack of adequate protein stability in solution may ultimately require development of an alternative, more complex formulation ...”).

C. The ’992 Patent

The ’992 patent is directed to formulations for the intravitreal administration of VEGF antagonists. Ex.1001, 1:30-37. The inventors of the ’992 patent

succeeded in achieving formulations of VEGF antagonists with increased stability.

Id. at 1:39-62. In doing so, the inventors overcame the various formulating challenges discussed above and developed a formulation with low propensity to aggregate under refrigerated conditions.

Reflecting this success, the '992 patent's two independent claims, Claims 1 and 10, both recite a vial or formulation comprising a VEGF antagonist, an organic co-solvent, a buffer, a stabilizing agent, and a particular stability-related property: at least 98% of the VEGF antagonist must be present in native conformation following storage at 5°C for two months, as measured by size exclusion chromatography. Ex.1001, 19:31-35, 19:41-43. Claims 1 and 10 also recite that the VEGF antagonist is a fusion protein that is produced in a Chinese Hamster Ovary ("CHO") cell and comprises an immunoglobulin-like ("Ig") domain 2 of a first VEGF receptor, an Ig domain 3 of a second VEGF receptor and a multimerizing component. *Id.* at 19:36-40. The dependent claims recite additional limitations for percent fusion protein present in native conformation in the formulation (99%, rather than 98%, in Claims 2 and 11), particular VEGF receptors (Claims 3 and 12), a particular VEGF antagonist amino acid sequence (Claims 4 and 13), the VEGF antagonist in dimer form (Claims 5 and 14), and specific organic co-solvents and stabilizing agents (Claims 6, 7, 8, 9, 15, 16, 17, and 18). Ex.1001 at 19:44-64, 20:41-65.

III. THE ASSERTED GROUNDS

The Petition includes two grounds. Ground 1 is alleged anticipation by Fraser (Ex.1009) alone. Ground 2 is alleged obviousness based on seven different references: Fraser, Wulff (Ex.1016), Holash (Ex.1010), the '319 Publication (Ex.1029), the '309 Publication (Ex.1027), McNally 2000 (Ex.1013), and FDA Container Closure Guidance (Ex.1038). The references referred to by Petitioner as “Key Prior Art,” Pet. 23, are summarized below.

A. Fraser (Ex.1009)

The Fraser paper reports on studies of the effects of intravenous dosing of a VEGF antagonist that it refers to using the terms “VEGF Trap” or “VEGFTrap_{R1R2}” on ovarian function in macaques (a type of monkey). Ex.1009, 1114, 1115, 1121-22. Fraser does not identify the specific protein used; it does not provide the nucleic acid or amino acid sequence of the VEGF antagonist, noting only that it “compris[es] Ig domain 2 of human VEGF-R1 and Ig domain 3 of human VEGF-R2, expressed in sequence with the human Fc.” *Id.*, 1115.

Fraser also specifies that this “VEGF Trap” 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,” without specifying which of the two final

ingredients was used. *Id.* Nor does Fraser describe what host cells were used to produce any of the VEGF proteins described.

As Petitioner admits, Fraser does not disclose that any of the formulations it recites would result in “at least 98% or [99%] of the VEGF antagonist [being] present in native conformation following storage at 5°C for two months as measured by size exclusion chromatography.” Ex.1001, 19:30-45; Pet. 1-2.

B. Wulff (Ex.1016)

Like Fraser, Wulff reports on the results of administering a VEGF antagonist—this time subcutaneously to marmoset monkeys—on ovarian function, and like Fraser, it describes the VEGF antagonist only as “VEGF Trap,” “VEGF Trap R1R2,” “VEGF R1R2,” or just “R1R2.” *Id.* at 2797, 2801-04, 2805, 2806. Wulff does not further identify the specific molecule used and does not provide the nucleic acid or amino acid sequence of the VEGF antagonist, stating only that it “compris[es] 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 IgG.” *Id.*, 2798.

C. Holash (Ex.1010)

Holash (Ex. 1010) is cited in the “Statement of Related Art” section of the ’992 patent and is “specifically incorporated by reference in [its] entirety.” Ex.1001, 1:47-52. Holash discloses pre-clinical trials that assessed the

pharmacokinetic and pharmacodynamic properties of several “VEGF-Trap” fusion proteins. Ex.1010, 11393. These included proteins that were termed VEGF-Trap_{ΔB1} (omitting VEGFR1 domain 3), VEGF-Trap_{ΔB2} (omitting VEGFR1 domains 1 and 3), and VEGF-Trap_{R1R2} (in which “the second Ig domain of VEGFR1 is directly fused to the third Ig domain of VEGFR2”). *Id.*, 11393-95. Holash does not provide further specificity on the identity of these proteins, such as a description of any bridging sequences between the domains or their amino acid or nucleic acid sequences.

D. '319 Publication (Ex.1029)

WO 00/75319 A1 (the “'319 Publication”) describes “Flt1 receptor polypeptides that have been modified in such a way as to improve their pharmacokinetic profile.” Ex.1029, 1:14-16. Among those modified proteins are two fusion proteins that the '319 Publication describes as “R1R2.” Ex.1029, 59:4-7. Both those fusion proteins comprise a human VEGF-R1 domain 2, a human VEGF-R2 domain 3, and a portion of the Fc region from an IgG1 antibody. Therefore, both proteins qualify as an “R1R2” VEGF Trap, despite several structural differences between the two proteins. *Id.* at 67:7-17. Unlike the references above, the '319 Publication discloses sequences for the two R1R2 proteins (named “Flt1D2-Flk1D3-FcΔC1(a)” and “VEGFR1R2. FcΔC1(a)”),

revealing that they have different bridging sequences *between* the above-listed domains. *Id.*; Ex.2001 ¶¶ 36, 46-50.

E. '309 Publication (Ex.1027)

U.S. Patent Publication No. 2004/0265309 (the "'309 Publication") "relates to methods of promoting regression of tumors and metastases by inhibiting vascular endothelial growth factor (VEGF) activity." Ex.1027 ¶ 2. It is not cited by Fraser, Wulff, Holash, the '319 Publication, or the '992 patent.

IV. EXAMINATION OF THE '992 PATENT APPLICATION

The '992 patent issued from an application filed on October 12, 2018. Ex.1004, 100. On April 2, 2019, the Examiner rejected the claims that are now challenged in the Petition based on, *inter alia*, non-statutory double patenting over five patents and applications: U.S. Patent Nos. 8,092,803; 7,608,261; 9,340,594; 9,914,763; and U.S. Patent Application No. 15/879,294. Ex.1004, 76-79. On July 22, 2019, Regeneron responded by filing a terminal disclaimer with respect to U.S. Patent No. 8,092,803. Ex.1004, 96. Regeneron also amended the pending claims to include an element relating to the stability of the protein conformation in storage over a period of time, a limitation that Regeneron explained was not found in any of the cited art. Ex.1004, 93. Regeneron further distinguished the pending claims from certain cited art that did not describe production in CHO cells. Ex.1004, 93-94. On August 21, 2019, the Examiner withdrew the non-statutory

double patenting rejection and allowed the pending claims based on the amended claims and terminal disclaimer. Ex.1004, 110. The '992 Patent issued on November 5, 2019. Ex.1004, 124.

V. LEVEL OF ORDINARY SKILL IN THE ART

For purposes of this Preliminary Response, Patent Owner has used Petitioner's definition of the POSA. Patent Owner reserves the right to propose another definition if review is instituted.

VI. CLAIM CONSTRUCTION

For purposes of this Preliminary Response only, Patent Owner does not challenge Petitioner's proposed constructions, because Petitioner has failed to show a reasonable likelihood of prevailing on any ground even under its own constructions. Patent Owner reserves the right to propose alternative or additional constructions at a future date if review is instituted.

VII. THE BOARD SHOULD DENY INSTITUTION BECAUSE PETITIONER FAILS TO SHOW A REASONABLE LIKELIHOOD THAT ANY CHALLENGED CLAIM IS ANTICIPATED OR OBVIOUS

A. The Prior Art Grounds Are Missing Multiple Challenged Claim Elements

1. Petitioner Does Not Show that the Fusion Proteins Described in Fraser and Wulff Meet the Native Conformation Limitation

Petitioner relies on Fraser (for Ground 1) and both Fraser and Wulff (for Ground 2) as allegedly disclosing a fusion protein and formulation that meet the

claim requirements. But each challenged claim contains a stability limitation that Petitioner admits is *not* found in those references (or anywhere else in the prior art). Ex.1001, 19:30-43 (“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”); Pet. 1 (“*Fraser* and *Wulff* are silent as to the percentage of the aflibercept [sic¹] in Regeneron’s prior-art formulation that would have remained in native conformation after two months’ storage at 5°C”); *id.* at 46 (same as to *Fraser*); Ex.1002 ¶ 96 (“*Fraser* does not explicitly disclose a percentage of the aflibercept [sic] (VEGFTrap_{R1R2}) that remained in native conformation in its formulation after storage at 5 °C for two months”).

Petitioner instead attempts to satisfy its burden by contending that a patent that Petitioner agrees is not prior art, *Dix* (Ex.1021), discloses data about the same fusion protein and formulation purportedly used in the studies described by *Fraser* and *Wulff*. Pet. 24 n.3 (“Petitioner does not offer *Dix* as prior art here but instead offers *Dix* ‘to elucidate what the prior art consisted of.’”); Ex.1002 ¶ 96. But the crucial assumption behind Petitioner’s argument—that the native conformation data in *Dix* corresponds to the same protein and formulations referenced in *Fraser*

¹ As discussed below, neither *Fraser* nor *Wulff* mentions aflibercept at all, nor do they contain any disclosure that the fusion protein they described is aflibercept.

and Wulff—is unsupported. The Petition therefore does not identify any stability data about the actual fusion proteins and formulations referenced in Fraser or Wulff, which is fatal to the Petition.

a. Both Fraser and Wulff Refer to the Their Fusion Proteins as “VEGF-Trap_{R1R2},” While Dix Reports Results for One Specific Protein Sequence

The data that Petitioner relies on in Dix is specifically for a VEGF antagonist with the amino acid sequence labeled “SEQ ID NO:4,” which Petitioner calls aflibercept in its Petition. Ex.1021, 10:43-49, 17:1-19:20. That stability data thus only pertains to the VEGF fusion proteins that are the subject of Fraser and Wulff *if* it can be shown that Fraser and Wulff *necessarily* concern aflibercept.

Petitioner fails to make this showing. As noted above, Fraser describes the administration of a VEGF antagonist to macaques, and refers to that antagonist only as “VEGF Trap” or “VEGF Trap_{R1R2}.” *E.g.*, Ex.1009, 1114, 1115, 1118. Wulff likewise refers to either “VEGF Trap,” Ex.1016, 2797-98, “VEGF Trap R1R2,” *id.*, 2797-98, 2804-06, “VEGF R1R2,” *id.*, 2806, or just “R1R2,” *id.*, 2800-05. Neither reference mentions the word “aflibercept” or provides a nucleic

acid or amino acid sequence for the administered VEGF antagonist.² And as shown below, “VEGF-Trap_{R1R2}” was not an alternative name specific and unique to aflibercept. The shelf life of the native conformation of the fusion proteins used in the formulations described in Fraser and Wulff is therefore unknown.

b. “VEGF-Trap_{R1R2}” or “R1R2” Refers to a Genus of Fusion Proteins, Not Just Aflibercept

Both Fraser and Wulff set forth the broad structural characteristics needed to qualify as a “VEGFTrap_{R1R2}” or “R1R2,” which is a genus of fusion proteins, not a single molecule. Ex.2001 ¶¶ 39-43. Fraser explains that “VEGFTrap_{R1R2}” is “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 Fc.” Ex.1009, 1115. (Hence the name “R1R2”—the protein contains a domain from VEGF receptor 1, also known as “R1” or “Flt1” and a domain from VEGF receptor 2, also known as “R2,” “Flk1,” or “KDR.”) Wulff likewise explains that “[t]he VEGF Trap R1R2 used in these experiments is a recombinant chimeric protein comprising portions of the extracellular, ligand binding domains of the

² Wulff states that more details on the VEGF antagonist are provided in the ’319 Publication, Ex.1016, 2798 n.1, but as discussed in the next subsection, the ’319 Publication describes *multiple different* VEGF sequences that fall under the “R1R2” label.

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 IgG....” Ex.1016, 2798.

Wulff also cites to the ’319 Publication, which makes clear that R1R2 refers to a *genus* of proteins that meet the characteristics above. In particular, the ’319 Publication characterizes two specific fusion proteins—called Flt1.D2.FlklD3.FcΔC1(a) and VEGFR1R2-FcΔC1(a)—as “R1R2” proteins that satisfy the structural characteristics set forth in Fraser and Wulff, but in fact, have different amino acid sequences. Ex.1029, 58:22-59:10. As their names indicate, both “R1R2” proteins are composed of “Ig domain 2 of Flt1 (VEGFR1)” (denoted R1 or Flt1D2) and “Ig domain 3 of Flk1 (VEGFR2)” (denoted R2 or FlklD3) expressed in sequence with a human Fc antibody constant region (denoted FcΔC1(a)).³ Thus, both Flt1.D2.FlklD3.FcΔC1(a) and VEGFR1R2-FcΔC1(a) are “R1R2” VEGF Traps, and both satisfy the structural descriptions given in Fraser and Wulff.

³ Although the antibody constant region is not specified in the above-quoted passage, the paragraph describes modifications to a protein known as “Flt1(1-3)-Fc,” which as the name indicates, consists of domains 1-3 of Flt1 in sequence with a human Fc. *See id.* at 50:23-24, 51:5-12.

But these two R1R2 proteins are distinct fusion proteins, with different amino acid sequences, as shown by the '319 Publication. The nucleotide and deduced amino acid sequences for Flt1.D2.Flk1D3.FcΔC1(a) are listed in Figures 21A-21C, *id.* 21:16-17, while those of VEGFR1R2-FcΔC1(a) are listed in Figures 24A-24C, *id.* 22:1-2. When aligned, they show the differences highlighted below:

Score	Expect	Method	Identities	Positives	Gaps
930 bits(2404)	0.0	Compositional matrix adjust.	455/461(99%)	455/461(98%)	6/461(1%)
Query 1		MVSYWDTGVLLCALLSCLLLTGSSSG-- --GRPFVEMYSEIPEIIHMTEGRELVIPCRVTS			57
Sbjct 1		MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTS			60
Query 58		PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIIISNATYKEIGLLTCEATVNGHLYKTNYLT			117
Sbjct 61		PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIIISNATYKEIGLLTCEATVNGHLYKTNYLT			120
Query 118		HRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELNVGIDFNWEYPSSKHQHKKLVNDRD			177
Sbjct 121		HRQTNTIIDVVLSPSHGIELSVGEKLVNCTARTELNVGIDFNWEYPSSKHQHKKLVNDRD			180
Query 178		LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKGPGDKTHTC			237
Sbjct 181		LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEK-- --DKTHTC			237
Query 238		PPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN			297
Sbjct 238		PPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN			297
Query 298		AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP			357
Sbjct 298		AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP			357
Query 358		QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL			417
Sbjct 358		QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL			417
Query 418		YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK		458	
Sbjct 418		YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK		458	

Ex.2001 ¶¶ 46-47. The “Query” sequence above represents

Flt1.D2.Flk1D3.FcΔC1(a) (the “first R1R2 protein”), the “S[u]bj[e]ct” sequence

represents VEGFR1R2-Fc Δ C1(a) (the “second R1R2 protein”), and the sequence in between denotes amino acid residues that are common between the two sequences. *Id.* The alignment shows that (1) Flt1.D2.FlklD3.Fc Δ C1(a) (the first R1R2 protein) lacks three amino acids—“SDT” or serine-aspartic-acid-threonine—that are found in VEGFR1R2-Fc Δ C1(a) (the second protein) and (2) includes three additional amino acids—“GPG” or glycine-proline-glycine—that are not present in VEGFR1R2-Fc Δ C1(a) (the second R1R2 protein). *Id.* As the ’319 Publication indicates, difference (1) stems from the fact that VEGFR1R2-Fc Δ C1(a) (the second protein) preserves the final three amino acids of Flt1 (VEGFR1) *domain 1* (“SDT”), which Flt1.D2.FlklD3.Fc Δ C1(a) (the first R1R2 protein) lacks, while difference (2) stems from the fact that Flt1.D2.FlklD3.Fc Δ C1(a) (the first R1R2 protein) preserves an “SrfI site” (i.e., a site that can be cleaved by the SrfI enzyme) between two domains by retaining three amino acid residues (“GPG”) that are disrupted in VEGFR1R2-Fc Δ C1(a) (the second R1R2 protein). Ex.1029 at 51:5-12, 61:2-8, 67:4-15.

With respect to difference (1), Fig. 24A of the ’319 Publication, which gives the nucleic acid and amino acid sequence for VEGFR1R2-Fc Δ C1(a) (the second R1R2 protein), shows the additional “SDT” that is not found in

Flt1.D2.Flk1D3.FcΔC1(a). In the excerpt below, the end of the signal sequence⁴ is shown in pink, the beginning of Flt1 (VEGR1) domain 2 in orange, and the bridging “SDT” left over from Flt1 domain 1 in between is in grey:

```

          70          80          90          100          110          120
          *          *          *          *          *          *
ACA GGA TCT AGT TCC GGA AGT GAT ACC GGT AGA CCT TTC GTA GAG ATG TAC AGT GAA ATC
TGT CCT AGA TCA AGG CCT TCA CTA TGG CCA TCT GGA AAG CAT CTC TAC ATG TCA CTT TAG
T  G  S  S  S  G>
21_hFLT1 SIGNAL SEQ_26>
      S  D  T  G  R  P  F  V  E  M  Y  S  E  I>
      27_____30_hFLT1 IG DOMAIN 2_____40>

```

Ex.1029, Fig. 24A (annotations added); Ex.2001 ¶ 48. The '319 Publication explains that “Flt Ig domain 1 extends from nucleotide 79 to 393, ending with the amino acids Ser-Asp-Thr [denoted above as “SDT” in grey]. Flt1 Ig domain 2 extends from nucleotide 394 to 687 (encoding Gly-Arg-Pro [denoted above as “GRP” in orange] to Asn-Thr-Ile)....” Ex.1029, 51:5-12. VEGFR1R2-FcΔC1(a) has the same sequence as the fusion protein *for* which stability data is reported in Table 9 of Dix. *Compare* Ex.1021, col. 17-20 *with* Ex.1029, Fig. 24A-C. Thus, a POSA would understand from the disclosure of the '319 Publication that a fusion protein, like this one, includes the VEGFR1 domain 2 and VEGFR2 domain 3

⁴ A signal sequence enables a protein to find its correct location outside the cell membrane by tagging the protein for transport through the cell membrane and out of the cell. Ex.2001 ¶ 48 n.19.

expressed in sequence with a human Fc antibody constant region, but other fusion proteins may include the same domains and constant regions, but differ from one another in terms of additional sequences, such as a signal sequence or bridging sequences, that do not form part of these domains. Ex.2001 ¶ 50.

Similarly, in the excerpt below from Fig. 21B of the '319 Publication, which shows the nucleic acid and amino acid sequence for Flt1.D2.Flk1D3.FcΔC1(a) (the first R1R2 protein), the end of Flk1 (VEGFR2) domain 3 is highlighted in blue, and the beginning of the human Fc domain is highlighted in gold, with the SrfI site in green bridging the two domains without forming a part of either:



Ex.1029, Fig. 21B (annotations added); Ex.2001 ¶ 49. It has long been known that differences in these linking sequences can have large effects on the stability of the fusion proteins. Ex.2038, 1; Ex.2001 ¶¶ 63-65.

The differences above between the “R1R2” proteins pertain to bridging sequences between domains. Still other differences in “R1R2” proteins derive from the fact that the literature disclosed various different amino acid sequences

corresponding to VEGFR domain 2 and VEGFR domain 3, which are described as being part of the fusion proteins used. Ex.2001 ¶¶ 53-61. As a result, still more amino acid sequences—and therefore still more proteins—correspond to the schematic definition of the protein given in Fraser. *Id.* ¶ 60.

The existence of multiple, different R1R2 fusion proteins is further confirmed by Daly,⁵ a published Regeneron patent application. Ex.2013. It explains, for example, that:

- There are a *variety* of fusion proteins comprising “a fusion polypeptide comprising receptor components R1-R2-F, wherein R1 is vascular endothelial cell growth factor (VEGF) receptor component Ig domain 2 of Flt-1 (Flt1D2), R2 is VEGF receptor component Ig domain 3 of Flk-1 (Flk1D3) (also known as KDR), and F is a fusion component.” *Id.* ¶ 5.
- Even “[i]n the specific embodiments, R1 is amino acids 27-126 of SEQ ID NO:6, or 1-126 of SEQ ID NO:6 (including the signal sequence 1-26); or amino acids 27-129 of SEQ ID NO:8, or 1-129 of SEQ ID NO:8 (including the signal sequence at 1-26). In the most specific embodiments, R2 is amino acids 127-228 of SEQ ID NO:6,

⁵ U.S. Patent Publication No. 2006/0058234 A1.

or amino acids 130-231 of SEQ ID NO:8”—in other words, there are multiple amino acid sequences that are R1R2 VEGF Traps. *Id.* ¶ 32.

- The plasmid “pTE115” “w[as] constructed from a precursor of the parent VEGF trap, VEGFR1R2.FcΔC1(a) (SEQ ID Nos:7-8), in which the three amino acids glycine-alanine-proline served as a linker between the Flk1D3 and FcΔC1(a)” but “[i]n all other respects” was “identical to that of the VEGF trap, VEGFR1R2.FcΔC1(a)” and “was used in the construction of the VEGF mini-traps because the linker DNA sequence included a Srf I restriction endonuclease recognition sequence that facilitated engineering the VEGF trap.” *Id.* ¶ 70.

Nor is that the extent of the genus. Daly also describes a “mini trap” protein that is also referred to as an R1R2 fusion protein:

- “The VEGF receptor components of the VEGF mini trap consist of the Ig domain 2 of Flt-1 (flt1D2) (R1), the Ig domain 3 of Flk-1 (flk1D3) (R2) (together, R1R2[]). The term ‘Ig domain’ of Flt-1 or Flk-1 is intended to encompass not only the complete wild-type domain, but also insertional, deletional, and/or substitutional variants thereof which substantially retain the functional characteristics of the intact domain.... The term ‘functional equivalents’ when used in reference to R1 and R2, is intended to encompass an R1 and R2

domain with at least one alteration, e.g., a deletion, addition, and/or substitution, which retains substantially the same functional characteristics as does the wild type R1 and R2, that is, a substantially equivalent binding to VEGF. It will be appreciated that various amino acid substitutions can be made in R1 and R2 without departing from the spirit of the invention with respect to the ability of these receptor components to bind and inactivate VEGF.” *Id.* ¶¶ 29-30.⁶

Petitioner fails to acknowledge that the formulations disclosed in Fraser and Wulff could contain any of multiple proteins within the genus, and offers no reason why Fraser and Wulff would necessarily be understood by a POSA to be describing aflibercept specifically, rather than some other protein(s) in the genus.

c. The fact that the “VEGF-Trap_{R1R2},” “VEGF Trap R1R2,” or “R1R2” disclosed in Fraser and Wulff are genera precludes inherency

Because the R1R2 proteins used by the authors of Fraser and Wulff were unidentified members of a genus, it is unknown whether Dix is providing stability data for the same fusion protein or proteins that the authors administered or a different one within the same genus. Given that uncertainty, Petitioner has not established that the stability data reported in Dix corresponds to any of the

⁶ A “mini-trap” has a truncated multimerizing component. *Id.* ¶ 9.

formulations in Fraser and Wulff. There is no dispute that the native conformation limitations of the Challenged Claims are not found expressly in the prior art, and Petitioner’s failure of proof precludes any argument that these limitations are *inherently* disclosed. Inherency applies only when the prior art “must *necessarily* include [an] unstated limitation,” *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002), and “may not be established by probabilities or possibilities.” *In re Cortright*, 165 F.3d 1353, 1360 (Fed. Cir. 1999) (internal citations omitted).

In fact, there is positive evidence that Fraser and Dix did not involve the same protein and formulation. As Petitioner’s expert concedes in a footnote, “[t]he *Fraser* formulation and the *Dix* formulation have different lot numbers”—“[t]he *Dix* formulation is ‘VGT-FS405’ and the *Fraser* formulation is ‘VGTF01001T,’” suggesting that the proteins and/or formulations are *not* the same. Ex.1002 ¶ 101 n.6.⁷ That is consistent with the fact that “VEGF Trap,” “VEGF-Trap_{R1R2},” and “R1R2” are not alternative names specific and unique to aflibercept, but instead are

⁷ Dr. Tarantino contends that “the formulations are described as being part of the same project ‘VEGF-SS017,’” but in fact that number is nowhere to be found in Dix’s disclosure. *Id.*

general descriptions of genera of fusion proteins with certain common characteristics.

Petitioner has not even addressed that these are names for genera, much less argued that all members of the genus meet the native conformation limitations (as it must, in order to succeed in its inherency argument). Such an argument would be incorrect, because a POSA would not expect the differences among all of these different R1R2 fusion proteins to be inconsequential. It is well known that even small changes in the amino acid sequence of proteins can have large effects on their stability. Ex.2001 ¶¶ 63-68. As but one illustration, Sanfelice describes a protein that typically undergoes cold denaturation at 16.8°C, but changing only one amino acid residue resulted in it undergoing cold denaturation only at 3-4°C. *Id.* ¶ 67; Ex.2019, 2-3, Table 1. In other words, a change to only one amino acid residue allows a protein to be stored at 5°C when the wild-type could not be. Similarly, Yang describes a COVID spike protein where a single mutation increased stability when compared to the wild-type. Ex.2001 ¶ 68; Ex.2042.

This case is on all fours with *Amgen, Inc. v. Alexion Pharmaceuticals*, IPR2019-00741, 2019 WL 4132685 (P.T.A.B. Aug. 30, 2019). There, the prior art reference—Hillmen—“d[id] not expressly disclose the claimed antibody,” but “Petitioner relie[d] on the doctrine of inherency and a post-priority-date admission by Patent Owner that the pharmaceutical (eculizumab) referenced in Hillmen was

actually the claimed antibody.” *Id.* at *9. The Board rejected this argument because it found that “‘eculizumab’ referred to and refers to *a class or category*” of antibodies, only one of which satisfied the claim requirements. *Id.* (emphasis added). Relying on the Federal Circuit’s decision in *Endo Pharms. Sols., Inc. v. Custopharm, Inc.*, the Board explained that inherency could not be relied upon where the prior art disclosed “a product that was named, but not known or determinable based on the prior art disclosure of its performance characteristics.” *Id.* at *10 (citing 894 F.3d 1374, 1383 (Fed. Cir. 2018)). *Amgen* observed:

Hillmen’s mere reference to ‘eculizumab’ would have at least invoked the Thomas IgG4 isotype eculizumab [which did not meet the claim requirements], too. Thus, Hillmen’s disclosure of ‘eculizumab’ would not have necessarily led the skilled artisan to the claimed antibody....

Id. at *11. Because “Hillman’s mere reference to ‘eculizumab’” would have invoked antibodies that did not meet the claim requirements along with ones that did, “there [was] no inherent anticipation.” *Id.*

Similarly, in *Pharmacyclics LLC v. Alvogen*, the claim at issue recited “Form A,” a crystalline form of the BTK inhibitor known as ibrutinib. No. 2021-2270, 2022 WL 16943006, at *5 (Fed. Cir. Nov. 15, 2022). The prior art referred to “PCI-32765,” which at trial was found to refer to “ibrutinib generally, and not to any specific form of ibrutinib.” *Id.* It was shown at trial that every lot

of PCI-32765 used in the studies described in the prior art was, in fact, Form A. *Id.* Nevertheless, the Federal Circuit held that there was no inherent anticipation because “Form A was not *necessarily* present” in the prior art. *Id.* at *10 (emphasis added) (internal citation omitted).

So too here. Even assuming *arguendo* that Petitioner is correct that the fusion protein tested in Table 9 of Dix, appropriately formulated, would meet the native conformation limitations of the Challenged Claims, the prior art’s reference to “VEGF Trap,” “VEGFTrap_{R1R2},” “VEGF Trap R1R2,” or “R1R2” would have invoked fusion proteins that Petitioner has not even attempted to show would meet the native conformation limitation. The fact that these terms refer to a genus, rather than to the unique fusion protein tested in Dix, precludes Petitioner’s attempt to show that the recited limitations are inherently present. *See id.*

Rather than squarely confront the prior art disclosures, Petitioner and its expert attempt to blur the difference between “VEGF Trap,” “VEGF-Trap_{R1R2}” and aflibercept through alterations or parentheticals. *See, e.g.*, Ex.1002 ¶ 62 (referring to “VEGF-Trap_{R1R2} [aflibercept]” and “the VEGF-Trap [aflibercept]” in Holash, where alterations are *not* in the original); *id.* ¶ 61 (referring to “VEGF-Trap_{R1R2} (aflibercept)”); *id.* ¶ 64 (referring to “VEGFTrap_{R1R2}—aflibercept”). But Petitioner does not point to a single prior art disclosure that states that the terms are

synonymous, and, as shown above, the evidence is to the contrary—the terms are not synonymous. Unsupported implication is no substitute for explicit disclosure.

d. Petitioner’s Reliance on Patent Owner’s Post-Priority-Date Statements Fails

Petitioner attempts to cure the lack of disclosure in the prior art using statements by Patent Owner from after the priority date. Pet. 14 n.1. But Patent Owner’s post-priority statements do not indicate that aflibercept is synonymous with the terms used in Fraser and Wulff as Petitioner contends. In any event, Patent Owner’s statements are not prior art, and therefore cannot be relied upon for anticipation or obviousness, because a POSA would not have the benefit of those statements as of the priority date when interpreting the disclosure in Fraser and Wulff.

First, the post-priority date statements that Petitioner relies on simply do not say what Petitioner argues they do. Petitioner relies on a statement from Regeneron to the patent office on December 22, 2011—more than five years after the ’992 Patent’s June 2006 priority date—stating 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}.” Pet. 14 n.1, Ex.1002 ¶ 64 (citing Ex.1020, 2); *see also id.* (stating that “aflibercept is described in [*Holash*] as VEGF-Trap_{R1R2}”). But the fact that aflibercept may sometimes be referred to by

the name of the genus to which it belongs does not mean reference to the genus refers *only* to aflibercept.

The fact that the sentence refers to “VEGF trap” further confirms that this is *not* the case, because even Petitioner tacitly concedes that “VEGF trap” refers to a genus of proteins, not any one specific protein. Pet. 26. Holash, for example, contains a section entitled “Engineering VEGF-Traps” and describes modifying a “parental VEGF-Trap” to create “VEGF-Trap_{ΔB1},” “VEGF-Trap_{ΔB2},” and others, yielding various “VEGF-Trap variants.” Ex.1010, 11393-94. The “parental VEGF-Trap” is clearly *not* aflibercept, since it “was created by fusing the first three Ig domains of VEGFR1 to the constant region (Fc) of human IgG1,” whereas aflibercept only contains domain 2 of VEGFR1. *Id.* 11393. Indeed, Holash is replete with references to the comparative performance of different proteins referred to as “VEGF-Traps” (plural). *Id.* 11395-96 (referring to “test[ing] these various VEGF-Traps” and “[u]sing blockade of VEGF-induced acute hypotension to pharmacodynamically compare VEGF-Traps”).

Similarly, Claims 4 and 15 of the '309 Publication, which Petitioner relies on as a prior art reference, requires that “the VEGF trap [be] selected from the *group* consisting of” various fusion proteins, demonstrating that “VEGF trap” (and similar terms) refers to a *genus*, not aflibercept specifically. Ex.1027, Claims 4, 15 (emphasis added); *see also* Ex.2013 ¶ 9 (defining “a VEGF ‘trap’” as being “a

multimeric VEGF-binding protein, comprising two or more fusion polypeptides of the invention”). That a beagle can sometimes be referred to as a hound does not mean that every reference to a hound necessarily refers only to a beagle and has the traits associated with a beagle.

Second, Patent Owner’s post-priority date statements cannot be relied upon to “fill in” missing disclosures in the prior art as a matter of law, even if they said what Petitioner wants them to say. In *Endo*, the Federal Circuit explained that inherency cannot be used to fill in a prior art reference’s missing disclosure to the identity of a compound. *See Endo*, 894 F.3d at 1378-79. In that case, the prior art described clinical trials for a drug formulation, which was later claimed in the patent at issue to be a formulation including a specific mixture of castor oil and benzyl benzoate. *See id.* The prior art, however, only mentioned the active ingredient, not the claimed mixture of castor oil and benzyl benzoate. *Id.* And even though the parties agreed that the prior art formulations did include the claimed mixture, because this could not be determined *purely on the basis of the information in the prior art*, there was no inherent disclosure, and the patent claims at issue were not obvious. *Id.* at 1381-83. The facts of *Endo* were even more favorable to the challenger than those here—there, it was acknowledged that the prior art was in fact describing the claimed mixture, even if the prior art articles did not say as much. The Federal Circuit’s holding that post-priority date evidence

could not be relied upon to establish the identity of a compound in the prior art thus applies with greater force here.

e. Petitioner's Reliance on the '319 Publication and the '309 Publication Fails

The disclosures of the '319 Publication and the '309 Publication do not help Petitioner, because neither establishes that Fraser or Wulff used “VEGF-Trap_{R1R2}” or similar terms to refer to—and only to—aflibercept. The '319 Publication in fact shows the opposite by confirming that “R1R2” and related terms refer to a *genus* of proteins, as discussed above. *See supra* Section VII.A.1.b. As for the '309 Publication, while it notes that “[i]n a specific and preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1 (a) (also termed VEGFtrap_{R1R2}),” the disclosures cited in the preceding section demonstrate that language like “also termed” is often used (consistent with the conventions of plain English) to mean that VEGFR1R2-FcΔC1(a) is *part of the genus* referred to as VEGFtrap_{R1R2}, as distinct from fusion proteins that include additional receptor domains.

Moreover, the '309 Patent is not referenced in either Fraser or Wulff, and cannot be used to supply what is lacking in those references. Again, *Amgen* is instructive. The Board in *Amgen* found no inherent anticipation where the prior art reference disclosed “eculizumab,” which the Board found was a genus of antibodies, not all of which met the claim requirements. *Amgen*, 2019 WL 4132685, at *11. There, the petitioner relied on three prior art references

(Bowdish, Evans, and/or Mueller) to show that Hillmen’s disclosure of “eculizumab” necessarily met the claim requirements. *Id.* at *7. The Board rejected that argument, noting that Hillmen cited another prior art reference (Thomas) that disclosed an eculizumab embodiment that did *not* satisfy the claim requirements. *Id.* at *11. By contrast, Bowdish, Evans, and Mueller were “not cited in Hillmen,” and thus, “such references’ teaching, even if considered ‘general knowledge,’” could not have “somehow overridden Hillmen’s direct invocation of Thomas’s disclosure of eculizumab so as to point the skilled artisan to some alternative antibody structure.” *Id.*

The same is true here. Wulff cites the ’319 Publication, which makes clear that VEGFTrap_{R1R2} is a *group* of fusion proteins, only one of which Petitioner asserts meets the claim’s native conformation requirements. Even if the ’309 Publication indicated that VEGFTrap_{R1R2} was the same as the aflibercept protein discussed in Dix (which it does not), under *Amgen* it cannot “overrid[e] [Wulff’s] direct invocation of” the ’319 Publication. *Id.* Indeed, Petitioner provides no reason why a POSA would have turned to the ’309 Publication to determine the identity of the VEGFTrap_{R1R2} molecules discussed in Fraser and Wulff at all: The ’309 Publication “relates to methods of promoting regression of tumors and metastases by inhibiting vascular endothelial growth factor (VEGF) activity,” Ex.1027 ¶ 2, rather than the construction of particular VEGF antagonists

that would be useful for either the purposes studied in Fraser and Wulff (suppression of ovarian function), Ex.1009, 1114; Ex.1016, 2797, or those that are the focus of the '992 patent (suitability for intravitreal injection into the eye and stability), Ex.1001, 1:30-37. Petitioner does not explain why anyone “would look to this particular art to solve the particular problem at hand.” *See Cir. Check Inc. v. QXQ Inc.*, 795 F.3d 1331, 1335 (Fed. Cir. 2015).

Because Fraser and Wulff do not disclose which protein in the VEGFTrap_{R1R2} genus was administered, there is no basis to conclude that Dix presents native conformation data for that protein. As such, there is no express or inherent disclosure of the required stability limitation in those (or any other) prior art references. Both Grounds of the Petition—which require assuming that the non-prior art data from Dix applies to the formulations described in Fraser and Wulff—therefore fail.

2. Petitioner Does Not Show that the Formulation Used in Fraser Meets the Native Conformation Limitation

Petitioner’s argument that Dix provides stability data for the fusion protein and formulation used in the study described by Fraser also depends on the assumption that the formulations used by the authors of Fraser are the same as those described in Dix. Again, Petitioner fails to show that that is the case.

Fraser discloses that the VEGF antagonist “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 (emphasis added). Dix, by contrast, discloses a formulation of “5 mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 25 mg/ml VEGF trap protein.” Ex.1021, 11:15-17. In short, Fraser does not make clear that it used “20% sucrose” as a stabilizer, as Dix did.

Petitioner attempts to fill this hole by pointing to a statement made by a Regeneron patent prosecutor in 2010 (after the priority date) in order to overcome a rejection over Fraser by stating that Regeneron had completed a formulation with “24.3 mg/mL VEGF Trap protein, 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 20% sucrose, and 0.1% polysorbate-20, pH 6.05, which is the actual lot and formulation used in Fraser.” Ex.1023, 2. But as noted above, *Endo* forbids using post-priority date information to supplement missing disclosures in the prior art. 894 F.3d at 1281-83; *see also Peaklogic*, IPR2022-01550, 26 (rejecting attempt to rely on attorney argument in prosecution history to supplement disclosures of prior art). One cannot simply assume, as Petitioner does, 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.

3. The References Do Not Disclose the Formulation Used by Wulff at All

The only other reference that Petitioner relies on for disclosure of a formulation that purportedly meets the claim requirements is Wulff, but Wulff does not disclose the formulation used with the VEGF antagonist at all. As noted above, Wulff describes an experiment in which marmosets were given a VEGF antagonist. Ex.1016. Wulff explains that “[c]ontrol animals were treated with [a] vehicle containing 5 mM phosphate, 5 mM citrate, 100 mM sodium chloride, 0.1% (wt/vol) Tween 20, and 20% (wt/vol) sucrose,” but it does not describe the specific formulation used for the experimental group, which received the VEGF antagonist. Ex.1016, 2798 (emphasis added).

Petitioner contends that “[a] POSA would have understood that the ‘vehicle’ referred to in *Wulff* contained aflibercept for the test animals and no aflibercept for the control animals, since the aflibercept could not have been injected into the animals unless it was dissolved within the vehicle.” Pet. 28; Ex.1002 ¶ 147. Petitioner’s speculation that the “vehicle” for both groups of marmosets was the same (except for the presence of VEGF antagonist) is unsupported by the record. For example, Petitioner’s own cited art, Fraser, discloses that while “VEGF Trap vehicle alone also was employed during some control cycles,” in other cases, “[h]uman Fc, for control treatments, was provided at a concentration of 19.7 mg/ml in buffer composed of 40 mM phosphate and 20 mM NaCl (pH 7.4).” Ex.1009,

1115. This formulation is different from the formulation used for the VEGF Trap protein. Ex.1009, 1115. Thus, in Fraser, the same vehicle was not used for the experimental and control animals, and Petitioner offers no reason to assume differently in Wulff.⁸

Moreover, even if the experimental group in Wulff did receive the VEGF antagonist in the same vehicle as that administered to the control group, Wulff does not disclose the concentration of VEGF Trap protein, and it is unknown whether the same concentration was used as in the Dix formulations. This is significant because, as Dr. Tarantino acknowledges, the concentration of the VEGF

⁸ Dr. Tarantino also implies that Wulff's lack of disclosure can be filled in using the formulation disclosed in Fraser, and that Fraser's own lack of disclosure as to the stabilizer (given its reference to the stabilizer being "either 20% glycerol or 20% sucrose") would have been filled in using Wulff's reference to 20% sucrose being used in the vehicle given to the control animals. Ex.1002 ¶ 147 & n.9. This mix-and-match approach to inherency, which essentially contends that the allegedly inherent limitation can be met if prior art conditions were optimized, is not permissible. *See In re Rijckaert*, 9 F.3d 1531, 1533-34 (Fed. Cir. 1993) (noting that "[w]hile the condition described may be an optimal one, it is not 'inherent' in [the prior art]").

Trap can affect its stability: “formulations with lower protein concentrations tend to exhibit *less* aggregation than ones with higher concentrations.” Ex.1002 ¶ 102 (citing Ex.1006, Table 6). Thus, Petitioner has not demonstrated what formulation was used in Wulff, much less that it was necessarily the same as that used in Dix, as inherency requires.

B. Ground 1 Fails Because the References Do Not Disclose that Fraser’s Protein Was Created in CHO Cells

Petitioner does not identify any description in Fraser of the host cells used to produce the VEGF Trap_{R1R2} protein discussed therein. There is none. Despite this lack of disclosure, Petitioner contends that “a POSA would have understood” that CHO cells were used. Pet. 45. But Petitioner fails to demonstrate that this is *necessarily* the case, which is fatal to anticipation and Ground 1.

Fraser does not describe the host cell(s) used: Fraser is silent about the host cell used to produce the VEGF Trap_{R1R2} provided by Regeneron to the Fraser authors for use in the experiments described therein. *See* Ex.1009, 1115.

Holash’s disclosures do not mean that Fraser *necessarily* used CHO cells: Holash, which is cited in Fraser, discloses that CHO cells were used for all of the “VEGF-Trap variants” discussed in *Holash*, Ex.1010, 11394. But Fraser does not incorporate Holash by reference or say that the VEGF Trap_{R1R2} used by the Fraser authors is the same as any of the VEGF-Trap variants described in Holash. Petitioner tries to sidestep that gap by characterizing Fraser as citing

Holash—reference 21 in Fraser—“when describing its [VEGF-Trap_{R1R2}] properties,” Pet. 45, but provides no support for the notion that *host cell information* was among the properties for which Holash is cited. *Plc v. Inguran*, IPR2021-01027, 2022 WL 17532274, at *8 (P.T.A.B. Dec. 8, 2022) (holding that in an anticipation challenge, Petitioner could not rely on disclosures from references cited in primary reference). Fraser’s references to Holash are not about how the VEGF Trap_{R1R2} protein was produced but are instead about other properties. *See, e.g.*, Ex.1009, 1115 (“Compared 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 **(21)**.” (emphasis added)). At the time, CHO cells were far from the only mammalian cell used in the industry for recombinant protein production. Ex.1017, 1393 (in addition to CHO, “other cell lines, such as those derived from mouse myeloma (NS0), baby hamster kidney (BHK), human embryo kidney (HEK-293) and human retinal cells have gained regulatory approval for recombinant protein production”). In addition, Daly described producing a VEGF antagonist (a “mini trap”) in *E. coli*, a prokaryotic system, Daly ¶ 43, which is also used to produce ranibizumab, Ex.2008, 4.

To show a reasonable likelihood of anticipation on this record, it was incumbent upon Petitioner to explain, with evidentiary support, why a POSA

would treat Fraser’s reference to Holash as a sufficient description of the host cell used to create the particular VEGF Trap_{R1R2} protein used in Fraser. That Fraser *might* have used proteins produced from CHO cells is not sufficient for anticipation, and Petitioner fails to explain why this *necessarily must* be so. Both the Petition and Dr. Tarantino’s declaration simply repeat the above information and then jump to their desired conclusion. *See* Pet. 45-46; Ex.1002, ¶¶ 93-95. That is *ipse dixit*, not evidence. *See, e.g., Amazon.com, Inc. v. Jumpsport, Inc.*, IPR2018-00715, 2018 WL 4263376, at *19 (P.T.A.B. Sept. 6, 2018) (explaining that “conclusory testimony that does not provide the basis for the opinion is entitled to little or no weight”).

Wulff’s disclosures do not mean that Fraser *necessarily* used CHO cells:

Wulff is not cited in Fraser, and Petitioner does not contend otherwise. *See* Pet. 46. And Petitioner’s Ground 1 is an anticipation argument, not an obviousness argument. Wulff is thus not a part of Ground 1. *See Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1335 (Fed. Cir. 2002) (confirming rule that “anticipation does not permit an additional reference to supply a missing claim limitation”). Whether 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.⁹ *See Transclean Corp.*, 290 F.3d at 1373; *In re Cortright*, 165 F.3d at 1360.

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.

C. Petitioner Fails to Make a Threshold Showing that Any Challenged Claim Is Unpatentable for Obviousness (Ground 2)

Petitioner fails to show that the requirement of Claims 1 and 10 that 98% of the VEGF antagonist be present in native conformation following storage at 5°C for two months as measured by SEC would have been obvious.

Petitioner offers two arguments that the 98% native conformation limitation would have been obvious. First, Petitioner attempts to rely on inherency. Pet. 59.

⁹ There is also no merit to the argument advanced by Dr. Tarantino in a footnote that a POSA would understand the particular VEGF Trap_{R1R2} protein used in Fraser was the same as referred to in Wulff (and the '319 Publication referred to in Wulff) because manufacturers do not switch cell lines once a protein “has entered human clinical trials.” Ex.1002, ¶ 95 n.5. Fraser is not about human trials; it is about *animal* experiments conducted sometime prior to August 2004, Ex.1009. If anything, Dr. Tarantino’s opinions thus suggest that a POSA would understand that Fraser dates from when Regeneron had not settled on a preferred cell line.

Second, Petitioner argues that a person of skill in the art would have been motivated to make a commercial aflibercept product that was as stable as possible and would have expected to be able to achieve the claimed stability. Pet. 60-61.

Each argument fails.

1. Petitioner May Not Use Dix to Demonstrate Obviousness of the “98% Native Conformation Following Storage at 5°C For Two Months” Limitation Through Inherency

First, Petitioner attempts to repackaging its inherency arguments in the obviousness context, arguing, “[a]s explained in ... VII(A)1 above, Regeneron had already disclosed a formulation containing these ingredients, and a POSA would have viewed the use of such a formulation to be obvious. Merely claiming the results achieved by an obvious combination of ingredients does not distinguish that combination from the prior art.” Pet. 59 (citing *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977)).

But Petitioner cannot rely on inherency here. “[T]he use of inherency in the context of obviousness must be carefully circumscribed because ‘[t]hat which may be inherent is not necessarily known’ and that which is unknown cannot be obvious.” *Honeywell Int’l Inc. v. Mexichem Amanco Holding S.A. De C.V.*, 865 F.3d 1348, 1354 (Fed. Cir. 2017) (internal citation omitted). “What is important regarding properties that may be inherent, but unknown, is whether they are unexpected. All properties of a composition are inherent in that composition, but

unexpected properties may cause what may appear to be an obvious composition to be nonobvious.” *Id.* at 1355. *See also Dey, L.P. v. Teva Parenteral Meds., Inc.*, 6 F. Supp. 3d 651, 678 (N.D.W. Va. 2014), *aff’d sub nom. DEY LP v. Teva Parenteral Meds, Inc.*, 600 F. App’x 773 (Fed. Cir. 2015) (post-filing data of inherency “is not relevant to an assessment of whether the Asserted Claims were obvious” because it “would not have been part of the knowledge of a [POSA]”).

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. *See* Pet. 59, 61, 47-48. That argument was flawed for the reasons given in Section VII.A.1 above, but is doubly mistaken when advanced as part of Petitioner’s obviousness argument because Petitioner presents no evidence that the POSA would have known of this purported inherency at the priority date. The 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.

What is more, as discussed further below, Petitioner fails to show that a POSA would have expected the formulation of Petitioner’s asserted prior art combination to achieve 98% native conformation under the recited storage conditions. *See Honeywell*, 865 F.3d at 1355 (“What is important regarding properties that may be inherent, but unknown, is whether they are unexpected.”);

PAR Pharm., Inc. v. TWI Pharms., Inc., 773 F.3d 1186, 1195 (Fed. Cir. 2014) (claim not inherently obvious where the record lacked substantial evidence to establish that the POSA would have expected the inherent property); *see also* *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) (claim not inherently obvious where “[n]o expert testified that they foresaw, or expected, or would have intended, the reaction”).¹⁰

2. Petitioner Fails to Show that a POSA Would Be Motivated to Achieve “98% Native Conformation Following Storage at 5°C for Two Months.”

Petitioner 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.” Pet. 60. But Petitioner’s evidence demonstrates that a pharmaceutical

¹⁰ Petitioner relies on *In re Best* to argue that its inherency argument should apply to its obviousness ground. Pet. 59. There, the Board found that inherency properly applied in the context of an anticipation argument, and therefore found that it applied in the context of a single-reference obviousness argument as well. But here, Petitioner’s inherency argument is mistaken in the context of its anticipation argument, and Petitioner does not make a parallel single-reference obviousness argument. Further, no party in *Best* attempted to show inherency with non-prior art data.

formulator does not pursue only the goal of reducing aggregation, but rather balances competing priorities of preventing the many different forms of physical and chemical degradation while creating a formulation that is acceptable to patients. Ex.1006, 6 (“[I]t would be ideal to have a pure protein in an absolutely stable formulation. In reality, however, scientists have to design formulation based on compromises that deal with several different potential problems.”), 2, 4; Ex.2001 ¶¶ 25-27.

Thus, 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. Ex.1006, 2, 4, 6; Ex.2001 ¶¶ 25-27. Even the references that Petitioner relies on to argue that 98% native conformation was achievable for certain antibodies, Pet. 21-22, actually describe formulations as “stable” when a much lower fraction of the product—between 90% and 95%—was present in native conformation. Ex.1030, 8:31-33 (“[A] ‘stable’ formulation may be one wherein less than about 10% and preferably less than about 5% of the protein is present as an aggregate in the formulation.”); Ex.1026 [0063] (same); Ex.1024 [0036] (“The criteria for stability are as follows. No more than 10%, preferably 5%, of antibody monomer is degraded as measured by SEC-HPLC.”); Ex.1025 [0025] (same).

Other evidence shows that *less* than 98% in native conformation was a common target, contrary to Petitioner’s contention that a formulator would seek absolute stability, Pet. 60-61. For example, native conformation below 98% was consistent with certain generally applicable standards, *see* Ex.2014, 14 (FDA guidance applicable to “biotechnological/biological products” defining “significant change” in part as “[a] 5 percent change in assay from its initial value”), and certain product-specific standards as of the priority date, Ex.2021, 5 (U.S. Pharmacopeia monograph for Somatropin permitting as high as 4% high molecular weight protein components).

Petitioner ignores this evidence in favor of a platitude—100% stability is best “[i]n an ideal world.” Ex.1002, ¶ 81; Pet. 20 (relying on Ex.1002, ¶ 81). That failure to address what Petitioner’s own references disclose confirms that Petitioner has not met its burden of proof. *Apple Inc. v. Telefonaktiebolaget LM Ericsson*, IPR2022-00349, Paper 8, (P.T.A.B. Sept. 21, 2022) (denying institution solely based on petitioner’s failure to provide an adequate reason to combine or modify the asserted references).

3. Petitioner Has Not Shown a POSA Would Have Expected to Successfully Achieve at Least 98% Native Conformation Using the Formulation of Fraser

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.

Petitioner argues that Fraser's passing reference to the timeline on which the study drug was used would cause a POSA to conclude that achieving 98% native conformation at two months would be easily attainable. Petitioner reasons that a POSA would have chosen the formulation of Fraser based on the statement in Fraser that over the course of the study, "[a]ny compound remaining was stored at 4 C and used within 2 wk." Ex.1009, 1115; Pet. 58. This statement does not imply that the formulation would have maintained at least 98% native conformation after two months, or anything close to it. As discussed above, Petitioner's own references do not indicate that at least 98% native conformation is generally required for a protein to be useable; rather, they indicate that changes of 5% or more can be acceptable. Further, when aggregates form in significant quantities, they tend to form over time. Ex.2020, 4 (describing aggregation as a "slow" process following a lag time); *see, e.g.*, Ex.1021 at examples 1-3, and so usability at two weeks (in a single-injection animal trial) does not imply a high degree of stability over two months. And finally, adequacy of a formulation for a preclinical

study does not imply adequacy for clinical trials and approval. *See* Ex.1013, 147 (“If the objective of the initial phase I clinical trial is proof of concept, the simplest approach is formulation without a preservative.”); Ex.1006, 10 (“[i]n general, the addition of preservative(s), regardless of the preservative used, significantly changes the stability profiles of proteins”).

Further, because changes of a few amino acids can significantly affect a protein’s stability, Ex.2001 ¶¶ 63–68, Petitioner fails to show that a POSA would expect success using Fraser’s formulation with a particular VEGF Trap R1R2, such as aflibercept. Petitioner’s argument that a POSA would expect success using Fraser’s formulation (which Petitioner has failed to demonstrate includes aflibercept) with aflibercept as the active ingredient mirrors one the court rejected in *Cephalon, Inc. v. Watson Labs., Inc. (In re Armodafinil Patent Litig. Inc.)*, 939 F. Supp. 2d 456 (D. Del. 2013). There, Defendants asserted that a POSA would have understood the claimed polymorph “Form I” of armodafinil “has sufficient solubility and bioavailability when formulated into tablets or capsules,” because the prior art “describes the efficacious use of armodafinil pharmaceutical compositions in human clinical trials.” *Id.* at 499. But the court found no expectation of success, reasoning that the prior art reference “does not disclose the solid-state form of armodafinil used in its tablets and gel capsules or indicate that it consisted essentially of Form I.” *Id.* at 499-500.

Although Petitioner's reference McNally 2000 describes steps that a POSA generally might follow to try to achieve a stable formulation, Ex.1002, ¶¶ 156-59, McNally discloses that the steps of this "formulation study" will merely "allow the formulation scientist to determine *whether* a solution formulation will be acceptable for a given protein." Ex.1013, 139 (emphasis added). Petitioner fails to establish that the POSA would reasonably expect to actually achieve a formulation with at least 98% native conformation for any given protein.

Petitioner's evidence of *antibody* formulations with greater than 98% stability, Pet. 21-22, does not help. As discussed above, VEGF Trap is a fusion protein, and while it has some structural similarities to monoclonal antibodies, it includes domains from entirely different sources (VEGF receptors), which a POSA would not expect to exhibit the same stability. Ex.2016, 12; Ex.2017, 44. Moreover, while some monoclonal antibodies had been incorporated into stable formulations by 2006, it does not follow that a POSA would have had a reasonable expectation of success with respect to *any* recombinant protein, *see* Ex.2001 ¶¶ 22-24, 63-68; Ex.2020, 4, 6, especially given the relative novelty of fusion proteins as of the priority date; *see also* Ex.2001 ¶ 20; Ex.2009, 3-4 (describing fusion proteins as biologics "of the second generation era," and noting that far fewer fusion proteins than antibodies have been FDA approved).

VIII. THE BOARD SHOULD DENY INSTITUTION BECAUSE THE EXAMINER ALLOWED THE '992 AND A RELATED PATENT AFTER CONSIDERING THE ASSERTED ART

Petitioner relies on the same or substantially the same art that was considered during prosecution of the '992 Patent and of a continuation application with similar claims. Petitioner fails to demonstrate that, in considering the art, the Patent Office made any error material to the patentability of the challenged claims. Thus, discretionary denial under 35 U.S.C. § 325(d) is warranted.

A. The Same or Substantially the Same Art Raised by Petitioner Was Previously Presented to the Patent Office

Petitioner's primary reference for both Grounds 1 and 2, Fraser (Ex.1009), was cited in an 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. *Husky Injection Molding Systems, Ltd., et al., v. Plastipak Packaging, Inc.*, IPR2020-00428, Paper 24, 11 (P.T.A.B. July 28, 2020) ("*Husky*"). Despite this, and without explanation, Petitioner disagrees with the Examiner's reading of the art and asserts that because the Examiner did not make any rejections over the prior art during prosecution, "it is apparent that the Examiner did not consider the *Fraser* reference." Pet. 34. But as the Board has explained, "a rejection applying a reference that is later relied upon by a petitioner *is not a prerequisite* to a finding that such reference was already presented to the Office under § 325(d)." *Boragen, Inc. v. Syngenta Participations AG*, IPR2020-00124,

Paper 16, 21-22 (P.T.A.B. May 5, 2020) (emphasis added). Indeed, the Board has routinely exercised its discretion to deny institution based on prior art cited during prosecution that was not the basis for a rejection. *See, e.g., Husky*, Paper 24 at 11 (finding that a reference listed on an IDS met the first prong of the *Advanced Bionics* framework); *Fellowes, Inc. v. Treefrog Devs., Inc.*, IPR2020-01509, Paper 11, 7-8, 17 (P.T.A.B. Feb. 22, 2021) (denying institution based on § 325(d) because the prior art reference was considered by the Examiner as it was cited in an IDS and listed on the face of the patent); *Ocado Grp. PLC v. Autostore Tech. AS*, IPR2021-00412, Paper 9, 34-35 (P.T.A.B. July 21, 2021) (reference listed in IDS “was previously before the Office”); *Eyenovia, Inc. v. Sydnexis*, IPR2022-00963, Paper 7, 10-11 (P.T.A.B. Nov. 8, 2022) (similar) (denying institution). Petitioner’s conclusory—and legally incorrect—argument that Fraser was not considered should be rejected.

Turning to the additional references Petitioner relies on in Ground 2, Holash (Ex.1010) is expressly cited in the specification of the ’992 patent and incorporated by reference in its entirety. Ex.1001, 1:50-52. Thus, Holash was presented to the Patent Office. Petitioner does not assert otherwise.

For Dix (Ex.1021), Petitioner criticizes Regeneron for not “point[ing] the Examiner to *Dix*, which teaches the claimed stability limitations,” Pet. 33, but Petitioner states that it is not relying on Dix as prior art. Thus, it is not clear what

relevance Dix has to whether discretionary denial is warranted under § 325(d). In any event, Petitioner separately acknowledges that during the prosecution of priority applications relating to the '992 patent, the Examiner relied on a PCT publication related to Dix in making an obviousness-type double patenting rejection. Pet. 33-34. Indeed, the Examiner recognized that the formulations “taught by the Dix et al. reference have increased stability” (Ex.1039, 23), which is exactly what Petitioner relies on Dix (Ex.1021) to show. Petitioner fails to mention that in addition to being cited and referenced by the Examiner in the prosecution of parent applications to the '992 Patent, WO 2006/104,852 (to Dix et al.) (Ex.2022) and U.S. Patent Publication No. 2006/0217311 (to Dix et al.) (Ex.2023) were provided to the Examiner during prosecution of the '992 application and are cited on the face of the patent. *See* Ex.1001, cited references; Ex.1004, 87. These two publications include the same data as in the Dix patent on which Petitioner now relies¹¹ (no explanation is given for why Petitioner chose to

¹¹ Dix (Ex.1021) is related to a national phase application of PCT Publication WO 2006/104,852 (Ex.2022) and is a continuation of the application that published as U.S. Patent Publication No. 2006/0217311 (Ex.2023). All three references include the same stability data Petitioner relies on in Grounds 1 and 2. *Compare* Ex.1021, 12:5-20 *with* Ex.2022, [0049] *and* Ex.2023, [0053].

use Ex.1021 in its Petition instead of the Dix publications (Ex.2022 and Ex.2023) cited on the face of the '992 Patent). Therefore, the relevant portions of Dix, or material cumulative to them, were previously considered by the Patent Office.

Wulff (Ex.1016) and the '319 Publication (Ex.1029) were not cited during prosecution of the application that resulted in the '992 patent. However, Wulff is largely cumulative of Fraser. Ex.1004, 61, 87. Both Wulff and Fraser disclose effects of a VEGF antagonist on the reproductive system of primates. Petitioner asserts that Wulff “used the same formulation as in *Fraser*,” but also discloses using CHO cells to produce the VEGF antagonist. Pet. 35. But this minor difference in the disclosure between Wulff and Fraser is not enough to make Wulff non-cumulative, particularly where Petitioner separately relies on Holash (which Petitioner does not address in its discussion of §325(d)), for its disclosure of CHO cells. Pet. at 45-46.

The Board has found that substantially the same prior art was previously presented to the Office when the asserted references are cumulative of references provided to the Examiner in an IDS. *NXP USA, Inc. v. Impinj, Inc.*, IPR2020-00519, 2020 WL 4805424, at *3-5 (P.T.A.B. Aug. 17, 2020); *Gardner Denver, Inc. v. Utex Indus., Inc.*, IPR2020-00333, 2020 WL 4529832, at *5 (P.T.A.B. Aug. 5, 2020). As discussed above, Wulff is cumulative of Fraser and Holash, both of which were before the Patent Office during prosecution of the

'992 application, which provides further support for a discretionary denial. *See, e.g., Glaxosmithkline Consumer Healthcare Holdings (US) LLC v. Cipla Ltd.*, IPR2020-00370, Paper 7, at 9-12 (P.T.A.B. July 31, 2020) (petition relying on reference “not before the Examiner during prosecution” for two grounds still raised “substantially the same prior art,” as it did not “differ ‘in any material way from the art and arguments already considered and overcome during prosecution.’” (quoting preliminary response)).

Further, Petitioner omits the fact 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, Ex.2026.

Importantly, this patent includes claims with similar scope to those at issue here. A comparison of challenged Claim 1 of the '992 patent is presented below next to Claim 1 from the '458 patent to show the similarities in claim scope:

'992 Patent	'458 Patent
1. A <u>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 immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a</u>	1. A glass <u>vial comprising an ophthalmic formulation suitable for intravitreal administration comprising: a vascular endothelial growth factor (VEGF) antagonist fusion protein, an organic co-solvent, a buffer, and a stabilizing agent; wherein said VEGF antagonist fusion protein is glycosylated and comprises an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor that is human Flt1 and Ig domain 3 of a second</u>

'992 Patent	'458 Patent
<u>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.</u>	<u>VEGF receptor selected from the group consisting of human Flk1 and human Flt4, and a multimerizing component; and wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C for two months as measured by size exclusion chromatography.</u>

Ex.1001, cl. 1; Ex.2026, cl. 1.

In such circumstances, the fact that Wulff and the '319 Publication were considered by the Patent Office during ongoing prosecution weighs in favor of discretionary denial. *See, e.g., Live Nation Ent., Inc. v. Complete Ent. Res. B.V.*, PGR2017-00038, Paper 11, 12, 15-18 (P.T.A.B. Jan. 16, 2018) (denying institution under 325(d) based on art and arguments made during prosecution of challenged patent's continuation application which had claims of "very similar scope" to the challenged claims); *Ivantis, Inc. v. Sight Scis., Inc.*, IPR2022-01529, 2023 WL 2588217, at *7 (P.T.A.B. Mar. 21, 2023) (denying institution under § 325(d) and finding that "the prosecution histories of [] patents [that issued from continuation applications from the patent at issue] ... [were] instructive concerning art presented to the Office and considered for purposes of a § 325(d) analysis.").

The '309 Publication was not cited during prosecution of the '992 patent, but its relevant disclosures are cumulative of the '319 Publication, which was before the Patent Office during the prosecution of the '458 patent. Throughout the

Petition, the two publications are grouped together to make the same point. Pet. 15 (acknowledging that the '309 Publication incorporates the '319 Publication “by reference in its entirety”); *see also id.* at 35, 46, 51, 64.

The final two references cited by Petitioner in Ground 2 are McNally 2000 and FDA Container Closure Guidance. Neither is described as “Key Prior Art” by Petitioner and both simply describe general knowledge of the POSA. McNally 2000 is only relied upon to show how a formulation scientist would allegedly design formulation development studies. Pet. 62. The FDA Container Closure Guidance reference is cited only for the point that the FDA recommended that injectable formulations be packaged in vials. Pet. 58. Patent Owner does not dispute that these two references would have been part of the general knowledge of a POSA. The general knowledge of a POSA “is always part of the obviousness analysis,” whether identified separately or not, *Evergreen Theragnostics, Inc. v. Advanced Accelerator Applications SA*, PGR2021-00002, Paper 9 at 6 n.4 (P.T.A.B. Apr. 14, 2021), and Petitioner’s characterization of these references as asserted art “weighs little” in the 325(d) analysis. *See Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp.*, IPR2020-00040, 2020 WL 2478503, at *6 (P.T.A.B. May 12, 2020) (finding *Advanced Bionics* step 1 met although one reference “was not cited during prosecution”); *Monolithic Power Sys., Inc. v. Volterra Semiconductor LLC*, IPR2020-01348, 2021 WL 838428, at *6-7

(P.T.A.B. Mar. 4, 2021) (denying institution and finding “additional secondary references added ... insufficient to refute the exercise of discretion under 35 U.S.C. § 325(d).”). As in *Mylan*, Petitioner’s reliance on McNally 2000 and FDA Container Closure Guidance is “minimal,” and “[n]one of Petitioner’s arguments on discretionary denial point to any material teaching” in these references. 2020 WL 2478503, at *6.

B. Petitioner Fails to Demonstrate that the Examiner Erred in a Manner Material to Patentability (*Becton, Dickinson* factors (c), (e), and (f)¹²)

Given that the same or substantially the same art as Petitioner relies on was previously presented to the Patent Office, the burden shifts to Petitioner to show that the Office erred in a manner material to the patentability of the challenged claims. “An example of a material error may include misapprehending or

¹² *Becton, Dickinson* factors: (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (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. See *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (P.T.A.B. Dec. 15, 2017).

overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims.” *Advanced Bionics, LLC, v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, 2020 WL 740292, at *3 n.9 (P.T.A.B. Feb. 13, 2020). “If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Id.* at *3.

The entirety of Petitioner’s analysis of whether the Patent Office erred is the statement that “through no fault of the examiner, the Office erred to any extent it evaluated *Fraser*.” Pet. 36. This conclusory statement cannot satisfy Petitioner’s burden to establish material error by the Examiner. *Autel Intelligent Tech. Corp., Ltd. v. Orange Elec. Co., Ltd.*, IPR2021-01545, 2022 WL 1094028, at *12 (P.T.A.B. Apr. 8, 2022) (denying institution under 325(d) and noting that “Petitioner’s conclusory argument ... also fails to demonstrate that the Office erred”); *Panduit Corp. v. Corning Optical Commc’ns LLC*, IPR2021-01562, 2022 WL 1094029, at *7 (P.T.A.B. Apr. 6, 2022) (denying institution under 325(d) and finding “Petitioner’s assertion of Examiner error in the Reply to be conclusory and non-persuasive” where “Petitioner cite[d] no evidence in support of its contention that the Examiner erred.”); *see also Universal Imaging, LLC v. Lexmark Int’l, Inc.*, IPR2019-01387, 2020 WL 959375, at *5 (P.T.A.B. Feb. 27, 2020) (“Although Petitioner is correct that the Examiner did not reject any claims of the ’921 patent

based on [the asserted reference], that is not the end of our analysis.”). Although the Examiner did not issue a rejection based on Fraser, this is insufficient to show material error. *Sony Interactive Ent. LLC v. Terminal Reality, Inc.*, IPR2020-00711, 2020 WL 6065188, at *5 (P.T.A.B. Oct. 13, 2020) (Petitioner’s argument that asserted references were not substantively evaluated or applied in a rejection failed to sufficiently identify Examiner error).

As discussed above, each of the remaining key prior art references was either cited during prosecution of the ’992 patent, cited during other relevant prosecution, or cumulative to such cited art. Petitioner does not allege material error by the Patent Office with respect to any of this other key prior art, and there is none. Moreover, Petitioner is foreclosed from raising any new arguments concerning error in a reply. *Koa Corp. v. Vishay Dale Elecs.*, IPR2019-00201, Paper 30, 77 (P.T.A.B. May 7, 2020) (“A reply that raises a new issue or belatedly presents evidence may not be considered.”).

For these reasons, the Board should exercise its discretion and deny institution under § 325(d).

IX. CONCLUSION

For the foregoing reasons, institution of the Petition should be denied, both on the merits and as an appropriate exercise of the Board’s discretion.

IPR2023-00462

Dated: April 25, 2023

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Certification of Word Count (37 C.F.R. § 42.24)

I hereby certify that this PATENT OWNER’S PRELIMINARY RESPONSE has 13,622 words (as counted by the “Word Count” feature of the Microsoft Word™ word-processing system), exclusive of “a table of contents, a table of authorities, mandatory notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing.”

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Certificate of Service (37 C.F.R. § 42.6I(4))

I hereby certify that the attached PATENT OWNER'S PRELIMINARY RESPONSE was served as of the below date via email on the Petitioner (by agreement) at the following correspondence address:

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