Filed on behalf of: Celltrion, Inc.
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case No. IPR2023-00462
Patent No. 10,464,992

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 10,464,992

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I. INTRODUCTION AND SUMMARY

Celltrion, Inc. ("Petitioner") respectfully requests *inter partes* review of claims 1-18 of U.S. Patent No. 10,464,992 ("*'992 patent*," EX1001), assigned to Regeneron Pharmaceuticals, Inc. ("Regeneron" or "Patent Owner").

The challenged claims of the '992 patent are anticipated and rendered obvious by Regeneron's own prior art and should never have issued. The claims encompass a formulation comprising the VEGF inhibitor protein, aflibercept, which Regeneron markets under the trade name EYLEA®, and three excipients that are commonly used to stabilize proteins like aflibercept: polysorbate 20, phosphate buffer, and sucrose. According to the claims, the excipients stabilize the aflibercept so that at least 98% (or, in certain dependent claims, 99%) remains in "native conformation" when measured by size-exclusion chromatography ("SEC") after the formulation is stored for two months at 5º C. This formulation is not novel. Regeneron's scientists used this very same combination of excipients in the formulation Regeneron used to conduct its initial *in vivo* studies of aflibercept. That formulation was disclosed in Regeneron's *Fraser* (EX1009) and *Wulff* (EX1016) publications years before the effective filing date of the '992 patent.

While *Fraser* and *Wulff* are silent as to the percentage of the aflibercept in Regeneron's prior-art formulation that would have remained in native conformation after two months' storage at 5º C, the stabilizing properties of its

particular combination of excipients are inherent to the formulation. Merely testing an old composition and "discovering" its properties does not make the composition newly patentable. *Schering Corp. v. Geneva Pharmaceuticals, Inc.,* 339 F.3d 1373, 1382 (Fed. Cir. 2003).

To the extent that Regeneron disputes that the claimed stabilizing properties are the natural result of its prior-art formulation, its own published test results confirm this inherency. *Dix* (EX1021), a Regeneron patent that published shortly after the '992 patent's effective filing date, disclosed that Regeneron had performed SEC testing of an aflibercept formulation with the very same ingredients. Regeneron's testing showed that greater than 99% of the aflibercept remained in "native conformation" when stored at 5º C for two months. Regeneron cannot reasonably dispute that two formulations with the same ingredients will have the same inherent properties revealed by its own testing submitted previously to the Office.

Even if Regeneron's prior-art formulation published in *Fraser* and *Wulff* does not anticipate the challenged claims, the claims would have been obvious from that formulation in light of other prior art. *Fraser*, *Wulff*, and *Holash*, another Regeneron prior-art publication, had disclosed that aflibercept was a superior VEGF inhibitor with great therapeutic potential. Regeneron's published excitement over aflibercept's best-in-class *in vivo* performance would have

motivated a skilled artisan to create formulations of the protein suitable for *in vivo* use as a therapeutic product. *Fraser* and *Wulff* disclose the very formulation that Regeneron itself used to administer aflibercept *in vivo*. Indeed, the Regeneron formulation was the *only* one disclosed in the prior art that had been used *in vivo*. Publication of the very formulation used by the creator of aflibercept, and the paucity of alternative formulations, would have provided ample motivation to select the Regeneron formulation.

The skilled artisan also would have reasonably expected success with Regeneron's formulation. The artisan would have reasonably expected the excipient combination to be compatible with aflibercept because Regeneron chose it for Regeneron's own *in vivo* studies. The artisan also would have expected the formulation to be stable enough for *in vivo* administration in light of *Fraser's* explanation that the formulation, when stored at 4º C, remained usable in Regeneron's *in vivo* studies for at least two weeks. This published compatibility and stability would have made the Regeneron formulation an obvious choice.

This obviousness is not negated by the fact that the prior art did not disclose two-month stability data for Regeneron's formulation. Again, the stabilizing properties of that formulation are inherent to it, and *Dix* shows that a skilled artisan who merely copied the Regeneron formulation from *Fraser* and *Wulff* and conducted routine SEC testing would have observed the claimed level of protein in

native conformation. This stability is the natural result of a combination of ingredients that is obvious from the prior art, and including the natural result as a claim element cannot make the combination non-obvious. *See, e.g., Persion Pharms. LLC v. Alvogen Malta Ops. Ltd.*, 945 F.3d 1184, 1190 (Fed. Cir. 2019) (noting that an obvious formulation cannot become non-obvious simply by testing it and claiming the result of the test).

But even assuming for argument's sake that the claimed level of natively-conformed protein is not the natural result of Regeneron's prior-art formulation, that formulation still renders the challenged claims obvious. As Petitioner's expert Dr. Tarantino explains, the artisan would have been motivated to achieve as stable a formulation as possible in order to achieve as long a shelf-life as possible for an eventual therapeutic product. The artisan would have applied routine optimization techniques to Regeneron's prior-art formulation and reasonably expected to achieve the claimed level of natively-conformed protein, because similar results had been achieved numerous times for proteins of similar size and complexity.

The '992 patent tacitly acknowledges that this optimization would have been routine, since it broadly claims millions of different and quite diverse combinations of protein and excipients but discloses only a handful of specific, very similar examples. Since the specification contains no express guidance as to how to adjust the claimed protein and excipient combinations in order to achieve the claimed

level of natively-conformed protein, the public is left to shoulder a mountain of routine SEC testing to sift through the millions of diverse, possible combinations to discern which of them meet the mark. As Dr. Tarantino explains, the SEC results in *Dix* show that in comparison to this laborious testing required by the patent, the effort that would have been required to optimize Regeneron's prior-art formulation—had any adjustment been needed—is trivial.

Petitioner respectfully submits this Petition and supporting expert declaration from Dr. Ralph Tarantino (EX1002), an expert in the formulation of injectable dosage forms with over 25 years' experience in the pharmaceutical industry, to apprise the Board of invalidating prior art. *See* EX1002, ¶¶1-17; EX1003. For the reasons set forth herein, Petitioner respectfully requests that the Board institute this petition for *inter partes review* and cancel the challenged claims.

A. Brief Overview of the '992 Patent

The alleged innovation of the '992 patent is a very broadly-framed recipe for stable formulations of aflibercept and other VEGF-specific protein antagonists comprising four ingredients: a VEGF antagonist produced in a CHO cell, an organic co-solvent, a buffering agent, and a stabilizer. EX1002 ¶¶44-46, 52. The patent describes the innovation as "[s]table formulations of a VEGF-specific protein antagonist" comprising a "VEGF 'trap' antagonist with a pharmaceutically acceptable carrier." EX1001, 1:66-2:2. The patent defines "VEGF antagonist"

very broadly as "includ[ing] fusion proteins capable of trapping VEGF." *Id.*, 6:9-12. The "pharmaceutically acceptable carrier" is also defined very broadly as comprising "one or more organic co-solvent(s)…a buffering agent…and optionally…a stabilizing agent." *Id.*, 2:19-24. That broad recipe can purportedly be used to prepare millions of different lyophilized and liquid formulations of "VEGF trap" protein ranging from 10 mg/ml to 80 mg/ml. *Id.*, 3:44-46.

This combination of VEGF antagonist and excipients is not patentably distinct from a thicket of patents to very similar formulations that Regeneron has assembled to delay biosimilar competition for its aflibercept product EYLEA® for as long as possible. Most of that thicket is subject to terminal disclaimers scheduled to expire in March of 2025. But in a bid to extend patent protection for EYLEA® for another 15 months, Regeneron refused to file a terminal disclaimer for the '992 patent and a related patent, U.S. Pat. No. 8,092,803 ("the '803 patent"), over its earlier-expiring patents. Instead, Regeneron added a limitation to the claims of both patents that it asserted made them non-obvious over the earlier-expiring claims. That limitation requires at least 98% (or, in certain dependent claims, 99%) of the aflibercept in the formulation to remain in "native conformation" as measured by SEC after two months' storage at 5º C.

But the '992 patent does not state that the claimed 98-99% storage stability is critical to the invention or explain how to achieve it for any formulation other

than the handful in the examples. EX1002 ¶47. While the patent notes that the VEGF antagonist "is preferably substantially free of protein contaminants *at the time it is used to prepare the pharmaceutical formulation*," it does not describe any critical level of natively-conformed protein that the formulation must achieve over time during storage. EX1001, 6:24-27 (emphasis added); EX1002 ¶48. The patent merely explains that "substantially free of protein contaminants" means that preferably at least 90%, and most preferably at least 99%, "of the weight of protein of the of the VEGF-specific fusion protein antagonist *used for making a formulation* is VEGF fusion protein antagonist protein." EX1001, 6:26-32 (emphasis added); EX1002 ¶48.

Similarly, while the patent explains that "[t]he fusion protein is substantially free of aggregates," *id.*, 6:32-33, it further explains that "'substantially free of aggregates' means that at least 90% of the weight of fusion protein is not present in an aggregate *at the time the fusion protein is used to prepare the pharmaceutically effective formulation*." EX1001, 6:33-37 (emphasis added); EX1002 ¶48..

And while the patent frames the allegedly-inventive formulation very broadly, the specification provides only eight examples, each of which contain the same combination of protein, buffer, stabilizer and one of two organic co-solvents. The eight examples include 20 to 50 mg/ml of aflibercept, *i.e.,* "VEGF Trap (SEQ ID NO:4)" protein, in combination with phosphate buffer a pH of 6.3, sodium

chloride, sucrose, and either polysorbate 20 (seven of the eight examples) or polyethylene glycol 3350 (one of the examples). EX1001, 8:8-12:27, 36-61; *see also* EX1002 ¶51. The concentrations of protein, buffer, sodium chloride and polysorbate 20 vary somewhat in several of the examples, but only within relatively narrow ranges. *Id.*, 8:8-12:27, Examples 1-8.

Like the description of the invention in the specification, the claims of the '992 patent are much broader than the examples. The "VEGF antagonist" of independent claims 1 and 10 is not limited to aflibercept. The independent claims encompass formulations containing *any* amount of VEGF antagonist comprising *any* amount of "an organic co-solvent, a buffer, and a stabilizing agent" at *any* pH. Independent claim 1 is representative and is reproduced below:

> 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.

EX1001, 19:30-43. Independent claim 10 is identical to claim 1, with the exception that the preamble recites "a formulation" instead of a "vial."

The application that issued as the '992 patent was filed on October 12, 2018, claiming benefit through a chain of applications to a provisional application filed more than 11 years earlier on June 16, 2006. EX1001, 1. The '992 patent's priority chain includes eight issued patents and the 2006 provisional application. *Id.* Five of those eight patents (including the four patents preceding the '992 patent) were each rejected for double patenting, and Regeneron filed one or more terminal disclaimers to receive an allowance. *See* EX1039, 14-15; EX1043, 16-17; EX1044, 11; EX1045, 17; EX1046, 10-11.

As with Regeneron's preceding formulation patents, the Examiner rejected the first-amended independent claims presented during prosecution for double-patenting over Regeneron's earlier-issued patents and a pending application. EX1004, 77. Those early claims included all limitations of the allowed claims except the "at least 98%" natively-conformed protein limitation. *Id.*, 2.

To overcome this rejection, Patent Owner added the "at least 98%" limitation and filed a terminal disclaimer over Regeneron's '803 patent, which

contained formulation claims with the same limitation and was not terminally disclaimed over the other three duplicative Regeneron patents cited by the examiner. To overcome double patenting over the remaining three patents and one pending application, Patent Owner argued that the claims of those patents and application were patentably distinct because they did not "include elements relating to the stability of the VEGF antagonist over time when stored[.]" EX1004, 90-92, 93-94; EX1002 ¶49. The Examiner then allowed the claims.

B. Brief Overview of the Scope and Content of the Prior Art

1. Background

a. VEGF Antagonists

VEGF is a naturally-occurring protein that regulates "angiogenesis," the process by which new blood vessels are formed. EX1002, ¶54. VEGF functions by binding to specific VEGF receptors on the surfaces of cells responsible for angiogenesis, thereby increasing their activity. *Id.*, ¶55. Two of the best-characterized VEGF receptors are VEGF receptor 1 (VEGFR1) also known as Flt1, and VEGF receptor 2 (VEGFR2) also known as Flk1. EX1015, 412; EX1002, ¶55. VEGFR1 and VEGFR2 both have an extracellular region consisting of seven domains to which VEGF binds. EX1016, 2798; EX1002, ¶55. Upon binding to VEGF via these extracellular domains, the VEGF receptors combine to form a dimer that is the active, cell-signaling form. EX1015, 412; EX1002, ¶55.

By 2005, VEGF had been identified as having a role in angiogenesis in tumors, which is necessary for tumor growth. EX1008, 968; EX1002, ¶56. Given their potential to inhibit tumor growth, a number of VEGF inhibitors had been developed as anti-cancer therapies. EX1008, 971; EX1002, ¶56. One of these was bevacizumab, a humanized monoclonal antibody that binds to VEGF and blocks its activity. EX1008, 967, 971; EX1002, ¶56.

VEGF inhibitors had also been developed to treat age-related macular degeneration (wet AMD), a disease characterized by proliferation of blood vessels in the retina of the eye. One of these was ranibizumab, a modified fragment of the bevacizumab antibody. EX1015, 411; EX1002, ¶56.

b. Aflibercept

Aflibercept, also known as "VEGF-Trap$_{R1R2}$", "VEGFR1R2-FcΔC1(a)," and "VEGF Trap-Eye," is a VEGF inhibitor developed by Regeneron. Aflibercept is a fusion protein of domain 2 of the human VEGFR1 receptor and domain 3 of the human VEGFR2 receptor, linked via the Fc domain of a human IgG antibody as shown below:

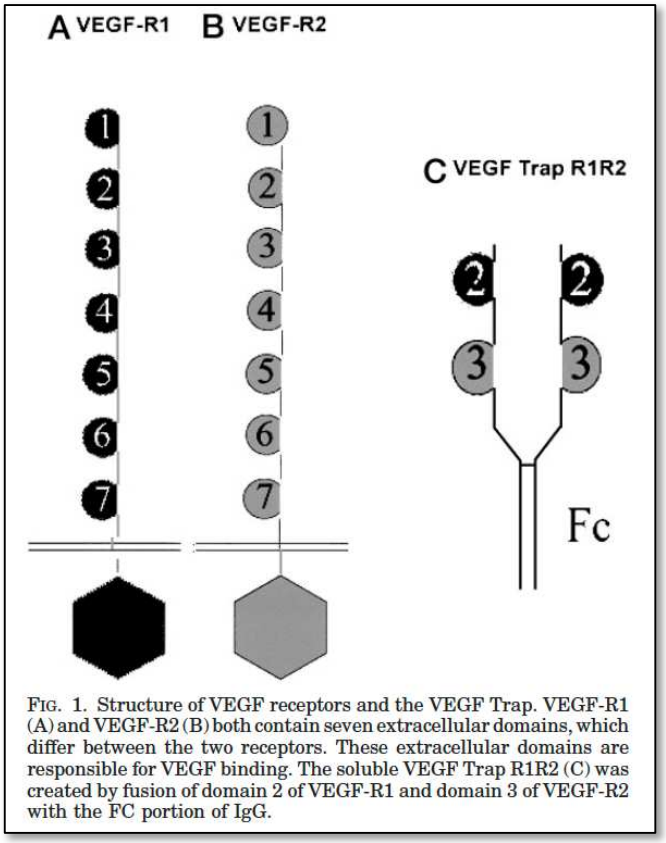

FIG. 1. Structure of VEGF receptors and the VEGF Trap. VEGF-R1 (A) and VEGF-R2 (B) both contain seven extracellular domains, which differ between the two receptors. These extracellular domains are responsible for VEGF binding. The soluble VEGF Trap R1R2 (C) was created by fusion of domain 2 of VEGF-R1 and domain 3 of VEGF-R2 with the FC portion of IgG.

EX1016, 2798, Fig. 1; EX1002, ¶57. Like bevacizumab and ranibizumab, it works by binding to VEGF and "trapping" it before it can bind to cell-surface VEGF receptors and trigger angiogenesis. EX1002, ¶58.

As early as 2002, Regeneron had published detailed descriptions of its development of aflibercept and *in vivo* experiments which demonstrated its superior therapeutic promise over other known VEGF inhibitors, including older VEGF-trap fusion proteins that Regeneron had been studying. EX1002, ¶59. For example, early in development, Regeneron had experimented with a recombinant "parental VEGF-trap" fusion protein in which the first three extracellular domains of the human VEGFR1 receptor were fused to the Fc region of human IgG1.

EX1010, 11393; EX1002, ¶¶59-60. This parental VEGF-trap had poor pharmacokinetics. EX1010, 11394-95, Fig. 1; EX1002, ¶60. Regeneron's scientists reasoned that this was due to the fact that certain of the extracellular domains of VEGFR1 were positively charged, which can lead to non-specific binding to negatively-charged components of the extracellular matrix in the tissue at the site of injection. EX1010, 11395; EX1002, ¶60. Regeneron then removed or replaced positively-charged domains to create less-positively-charged variants and found that this significantly improved pharmacokinetic performance. EX1010, 11395; EX1002, ¶61. Aflibercept emerged as the variant that had the best combination of *in vivo* pharmacokinetics and anti-VEGF activity, and compared favorably to other VEGF antagonists such as monoclonal antibodies. EX1002, ¶61. As Regeneron's scientists put it, "The combination of high-affinity and improved pharmacokinetics apparently contributes toward making VEGF-Trap$_{R1R2}$ [aflibercept] one of the most, if not the most, potent and efficacious VEGF blocker available." EX1010, 11397; EX1002, ¶62. Regeneron noted that aflibercept had the additional advantage of being composed of "entirely human sequences," which would "hopefully minimize the possibility that it might prove immunogenic in human patients." EX1010, 11397; EX1002, ¶62. In comparison to existing antibody VEGF antagonists, "far lower circulating levels of VEGF-Trap$_{R1R2}$ [aflibercept] are required for similar efficacy" and its "safety has recently been

confirmed in toxicological studies in cynomologus monkeys." EX1010, 11397; EX1002, ¶62. As a result of these superior properties "the [aflibercept] VEGF-Trap is currently in human clinical trials for several different types of cancer." EX1010, 11397; EX1002, ¶62.

By 2006, Regeneron had published initial positive data for its initial human clinical trials of aflibercept. EX1015, 414-15; EX1002, ¶63. Regeneron characterized the initial trial results as "quite promising" and noted that aflibercept was "now entering more advanced clinical trials in vascular eye diseases." EX1015, 414-15; EX1002, ¶63.

Regeneron had also widely published the sequence of aflibercept prior to the priority date, although it referred to the protein by its earlier scientific names, VEGF-Trap$_{R1R2}$ and VEGFR1R2-FcΔC1(a), rather than the non-proprietary name "aflibercept" it coined later as the molecule neared regulatory approval.[1] As early

[1] When obtaining a patent term extension for its patent 7,374,758 ("the *'758 Patent*") based on the regulatory approval of EYLEA®, Regeneron represented to the Office that aflibercept is "also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-Trap$_{R1R2}$." EX1020, 2, 6-7; EX1002, ¶64. Regeneron also represented that "aflibercept is described in [*Holash*] as VEGF-Trap$_{R1R2}$", EX1020, 5, and that the amino acid sequence of aflibercept is set forth in Figures 24A-24C

as 2004, Regeneron had published the amino acid sequences of VEGFR1R2-FcΔC1(a) in no fewer than three earlier patent publications. *See* EX1027, ¶5, SEQ ID Nos. 1 and 2 (disclosing that VEGFR1R2-FcΔC1(a) is "also termed VEGF-Trap$_{R1R2}$); EX1029, 12, 15, Fig. 24A-24C; EX1028, ¶8, SEQ ID Nos. 3 and 4; EX1002, ¶65. Regeneron also disclosed the sequence of VEGFR1R2-FcΔC1(a) in the *'758 Patent,* first published on November 3, 2005. EX1019, 10:15-17, Figs. 24A-24C; EX1002, ¶65.

In several of these same prior-art publications, Regeneron disclosed that it used a CHO cell host vector system to express aflibercept. *See, e.g.*, EX1029, 12, 15*,* Fig. 24A-24C, claims 9, 20 (describing and claiming the production of VEGFR1R2-FcΔC1(a) in CHO cells); *see also* EX1027 ¶22 (pointing the skilled artisan to the *'319 Publication* for "a complete description of VEGF-receptor based antagonists including VEGFR1R2-FcΔC1(a)" and incorporating the *'319 Publication* into the *'309 Publication* "by reference in its entirety."); EX1002, ¶¶66-67. *Wulff* disclosed that Regeneron made VEGF-Trap$_{R1R2}$ by expressing it in

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of the '758 patent. EX1020, 6-7 (noting that the "Flt1 Ig domain 2" of aflibercept "spans amino acid residues 27 through 129," "Flk1 Ig domain 3 spans amino acid residues 130 through 231," and "the Fc multimerizing component" spans amino acid residues 232 through 458"); EX1002, ¶64.

CHO cells. EX1016, 2798 and n.1 (explaining that "[t]he VEGF Trap R1R2 used in these experiments … was expressed in CHO cells" and pointing the reader to the *'319 Publication* for a description of "the detailed molecular structure" of VEGF-$Trap_{R1R2}$ and how it was created."); EX1002, ¶67. So did *Holash*. EX1010, 11394 (describing Regeneron's creation and testing of VEGF-$Trap_{R1R2}$ and related variants, and explaining that [a]ll of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells."); EX1002, ¶67.

c. Protein Stability

As of the priority date, it was well known that proteins like aflibercept were subject to physical and chemical degradation via well-defined pathways and mechanisms. *See, e.g.,* EX1005, 1; EX1002, ¶68.

Chemical instability refers to processes that break or form chemical bonds within the molecule. Examples of this type of instability include deamidation and oxidation. EX1002, ¶69.

Physical instability refers to processes that cause changes in the protein conformation, including aggregation and denaturation. EX1002, ¶69. Physical instability of a protein formulation is often manifested as the formation of microscopic clumps of protein known as aggregates. EX1005, 1. When formulating protein therapeutics, inhibiting aggregation is always a chief goal since aggregates can cause increased immunogenicity, alter the serum half-life of the

protein, and interfere with its function, *e.g.,* cause it to bind less well to its intended target at the site of disease. EX1002, ¶¶68-72.

There were many formulation techniques well known in the field that had proven to be effective in preventing protein aggregation. One common way was to include an organic co-solvent known as a "surfactant" in the formulation. *See* EX1006, Table 6; EX1002, ¶73. Aggregation often happens when the native folded structure of a protein destabilizes and "hydrophobic" (water-repelling) regions normally hidden in the interior of the protein become exposed to the surface. EX1002, ¶¶72-73. These hydrophobic regions will repel water but attract other hydrophobic substances, including hydrophobic regions on neighboring protein molecules. *Id*. This attraction will tend to cause destabilized protein molecules to adhere to each other. Surfactants are molecules with hydrophilic (water-loving) and hydrophobic ends that will orient their hydrophobic ends towards the hydrophobic portion of the protein and shield it from interacting with other proteins, thus preventing adhesion. *Id*.

Polysorbate 20 and polysorbate 80 (which were sold under the brand names "Tween 20" and "Tween 80," respectively) were commonly used surfactants to prevent aggregation in therapeutic protein formulations. *See, e.g.*, EX1014, Box 1; EX1002, ¶73. As of the priority date, a large number of FDA-approved and commercially-available protein therapeutics used polysorbate 20 or polysorbate 80

in their formulations to prevent aggregation. *See, e.g.,* EX1032, 2 (polysorbate 20); EX1034, 1117 (polysorbate 80); EX1037, 1359 (polysorbate 20); EX1033, 1350 (polysorbate 20); EX1036, 1338 (polysorbate 20); EX1002, ¶73.

Another well-known way to reduce aggregation was to use a hydrophilic sugar stabilizer such as sucrose. EX1002, ¶74. Solutions of protein therapeutic agents for administration by subcutaneous injection are often lyophilized (freeze-dried) to form solid powders in vials that can be reconstituted with suitable diluents such as saline prior to injection. *Id.* They are also commonly prepared as liquid protein formulations that are ready for injection. *Id.* To prepare these subcutaneous formulations, water must be removed by dehydration. It was well known that since hydrogen bonds between the surface of a dissolved protein and the surrounding water help to stabilize and preserve the protein's folded structure, dehydration can destabilize proteins. *Id.* It was also well known that hydrophilic sugar stabilizers like sucrose and trehalose can substitute for water by surrounding the protein and forming hydrogen bonds with its surface. *Id.* These hydrogen bonds stabilize the protein's folding, which reduces the exposure of hydrophobic interior regions of the protein and subsequent aggregation during storage. EX1005, 1, 2 ("formulation with carbohydrate excipients, such as sucrose and trehalose, has proven to be effective in the stabilization of freeze-dried proteins."); *see also* EX1014, 134; EX1002, ¶74.

As of the priority date, a number of approved and commercially-available protein products used disaccharides such as sucrose and trehalose as stabilizers in their formulations. *See* EX1032, 2 (trehalose); EX1034, 1117 (sucrose); EX1037, 1359 (sucrose); EX1033, 1350 (sucrose); EX1035, 2367 (sucrose); EX1036, 1338 (trehalose); EX1002, ¶74.

Another well-known way to stabilize protein formulations is to adjust pH, which can influence a large number of degradation mechanisms. EX1006, Table 7; EX1002, ¶75. It was well known that proteins are often stable against aggregation over narrow pH ranges and may aggregate rapidly in solutions with pH outside these ranges. EX1007, 1326; EX1002, ¶75. Optimization of pH was known to avoid certain other issues that could arise in formulation, such as structural changes driven by the strong positive and negative charges that can arise on the surface of a protein at certain pHs. EX1007, 1326; EX1002, ¶75. Buffers, which are mixtures of acid and base that tend to resist changes in pH, are used to maintain pH within a certain target range. EX1002, ¶76. Accordingly, "buffering" a formulation to keep pH at a value that minimized the effect of surface charges was a common technique to avoid protein degradation through this pathway. *Id.* Phosphate was among the most commonly-used buffers for proteins at the time, and a number of FDA-approved protein formulations were formulated with phosphate buffer prior to the priority date. *See* EX1032, 2; EX1034, 1117; EX1035, 2367; EX1002, ¶77.

Protein formulations are also refrigerated or frozen to avoid degradation. Protein degradation pathways were well known to proceed more slowly at colder temperatures. EX1002, ¶78. As a result, therapeutic protein formulations are commonly refrigerated at 2-8 °C to maintain stability. EX1032, 25; EX1034, 1121; EX1037, 1362; EX1033, 1352; EX1035, 2369; EX1036, 1341; EX1002, ¶78. In order to assess whether a formulation can be turned into a commercially-viable product that can be safely stored for a reasonable shelf life, it was common to test storage stability for weeks or months under refrigeration at 2-8 °C. *See, e.g.*, EX1026, ¶¶63, 280 (showing stability data for 1, 3, 14, 16, and 24 months); EX1002, ¶78.

At the time of invention, size-exclusion chromatography ("SEC") was among the most common techniques to quantify the formation of protein aggregates in a formulation over time. *See, e.g.*, EX1026, ¶278, Table 1; EX1012, 160; EX1002, ¶79. SEC measures differences in the size, molecular weight and shape of proteins, and is a commonly-used means of quantifying aggregation in a protein formulation over time. EX1002, ¶¶79-80.

The goal of a formulator seeking to optimize the utility and commercial value of a therapeutic biologic formulation is always to achieve 100% stability over a reasonable shelf-life. EX1002, ¶81. In practice, it was well-known as of 2005 that very high levels of purity can be maintained during refrigerated storage

at 2-8 °C. *Id.* As of the priority date, numerous publications reported formulations of antibodies that preserved >98% of the protein in "native conformation" as measured by SEC during storage at 5 °C for two months.[2] *Id.*, ¶82. Antibodies bear substantial physical and chemical similarities to aflibercept in that they are both large "Y"-shaped proteins in which the "arms" which bind to their targets are fused to Fc immunoglobulin (Ig) regions. *Id*., ¶¶70-71. *WO '801* (EX1030) discloses a number of lyophilized formulations of trastuzumab, a humanized antibody, that contained trehalose and polysorbate 20 and maintained >99% of the protein "intact" (*i.e.,* native conformation) as measured by SEC after storage at 5 °C for 2 weeks. EX1030, Table 4 (99.8% or 100.0% native conformation at 91 days), Table 5 (100.0% native conformation at 61 days), Table 6 (100.0% native conformation at 92 days), Table 7 (99.8% native conformation at 92 days); EX1002, ¶82. Similarly, *Kaisheva '316* reports SEC data for three formulations of

[2] The prior art sometimes refers to the results of SEC analysis as "% monomer" or "% intact protein" in the sample. As Dr. Tarantino explains, SEC is not an ideal tool to quantify monomeric protein. EX1002, ¶¶79-80. Nevertheless, the '992 patent and certain prior art did use SEC for this purpose. For clarity, the term "native conformation" will be used herein as that term is used in the '992 patent, *i.e.*, to refer to the % native conformation as measurable by SEC.

anti-IL-2 receptor antibody that utilized histidine, sucrose, and polysorbate 80. EX1024, ¶¶113-15, Fig 9A; EX1002, ¶83. At 3 months, all three formulations contained above 98% "monomer" (*i.e.*, native conformation). EX1024, ¶22; ¶¶113-15, Fig 9A; EX1002, ¶84. *Liu* reports two liquid formulations of recombinant human antibody that had >98% "monomer" (*i.e.*, native conformation) after storage at 5 °C for 3 months (and even up to 16 months). Both formulations contained polysorbate 20, and one protein formulation further contains trehalose. EX1026, ¶¶279-280; Table 1; EX1002, ¶85. *Kaisheva '417* reports a number of liquid formulations of dacilizumab antibody with greater than 98% "monomer" (*i.e.*, native conformation) after storage for 8 weeks at 5 °C. *See, e.g.*, EX1025, Table 5 (reporting 98.24% native conformation at 8 weeks storage at 5 °C), Table 6 (reporting 99.24% native conformation at 8 weeks storage at 5 °C), Table 8 (reporting 99.1% native conformation at 3 months storage at 5 °C), Table 9 (reporting 98.9% native conformation at 7 months storage at 5 °C), *see also* Table 10-13 (reporting similar results); EX1002, ¶86. The *'586 Patent* (EX1018) similarly reports an antibody formulation containing polysorbate 20 and trehalose as having >98% "monomer" (*i.e.*, native conformation) as measured by SEC after storage at 2-8 °C for two years. EX1018, Fig 28, 5:34-39; EX1002, ¶87.

2. Key Prior Art

a. Fraser (EX1009)

Fraser is titled "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function." EX1009, 1114. *Fraser* was published in the Journal of Clinical Endocrinology & Metabolism in November 2004. *Id.* November 2004 is more than one year prior to the '992 patent's earliest possible priority date of June 16, 2006 and thus *Fraser* qualifies as prior art under pre-AIA 35 U.S.C. 102(b) and post-AIA 35 U.S.C. 102(a)(1). *Fraser* lists Regeneron as an employer of at least one of the authors. *Id.*

Fraser's study was aimed at evaluating the effect of aflibercept on ovarian angiogenesis. *Id.*, 1114. In the study, macaque monkeys were given an injection of an aflibercept formulation that falls within each of the challenged claims: "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." *Id.*, 1115. "Tween 20" is brand name for polysorbate 20. EX1002, ¶¶91, 128; EX1011, 96.

Fraser reported that "VEGF was inhibited by administration of 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 Fc." EX1009, 1115.

b. *Dix (EX1021)*

The specification of U.S. Patent 8,110, 546 ("*Dix*"), assigned to Regeneron, was first published on November 4, 2010.[3] Regeneron represented during prosecution of *Dix* that the formulation used in *Fraser* contained sucrose rather than glycerol. EX1023, 2 (noting that the "actual lot and formulation used in

[3] Petitioner does not offer *Dix* as prior art here but instead offers *Dix* "to elucidate what the prior art consisted of." *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1330 (Fed. Cir. 2020.) In *Hospira*, the Federal Circuit considered the inherent disclosure of a prior art reference for the claimed property of "no more than about 2% decrease in the concentration" of an active ingredient in a pharmaceutical composition. *Id.*, 1326. The Federal Circuit admitted non-prior art evidence of the "no more than 2%" property because "[e]xtrinsic evidence can be used to demonstrate what is 'necessarily present' in a prior art embodiment even if the extrinsic evidence is not itself prior art." *Id*., 1329 (internal citations omitted). Here, Petitioner offers *Dix* to demonstrate the inherent properties of *Fraser's* formulation.

Fraser" contained "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.").

Table 9 of *Dix* discloses Regeneron's own stability testing of an aflibercept formulation that has the same ingredients as the one used in *Fraser*: "5 mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 25 mg/ml VEGF trap protein [VEGF-$Trap_{R1R2}$]" with pH ranging "from 6.0-6.1." EX1009 (*Dix*), 11:15-12:20, Table 9.

Table 9 of *Dix* show that 99.6% of the VEGF-$Trap_{R1R2}$ in the formulation remained in "native conformation" following storage at 5° C for two months as measured by SEC. *Id.*

c. Holash (EX1010)

Holash is titled "VEGF-Trap: A VEGF blocker with potent antitumor effects" and was published in the scientific journal Proceedings of the National Academy of Sciences on August 20, 2002. August 2002 is more than one year prior to the '992 patent's earliest possible priority date of June 2006 and thus *Holash* qualifies as prior art under pre-AIA 35 U.S.C. 102(b) and post-AIA 35 U.S.C. 102(a)(1). *Holash* lists Regeneron as an employer of at least one of the authors. EX1010, 11393.

Holash describes Regeneron's development of aflibercept. In particular, it discloses that an earlier, positively-charged "parental VEGF Trap" fusion protein

had poor pharmacokinetic properties that Regeneron postulated "might be due to the high positive charge of this protein (pI 9.4), which in turn may result in its deposition at the site of s.c. injection because of nonspecific adhesion to highly negatively charged proteoglycans that comprise the extracellular matrix." *Id.*, 11395. To test that theory, Regeneron "engineered several variants of the parental VEGF-Trap with reduced positive charges." *Id.* One of the variants was named "VEGFTrap$_{R1R2}$." *Id.* This variant "was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2" and had a lower positive charge. *Id.*, 11393, 11395. Beyond having a lower charge, Regeneron reasoned from prior structural studies that this structure would result in superior binding: "Previous structural analyses indicated that VEGFR1 might make greater use of its second Ig domain in contacting VEGF, whereas VEGFR2 instead makes greater use of its third Ig domain (26), raising the interesting and useful possibility that VEGF-Trap$_{R1R2}$ might actually bind more tightly to VEGF than the parental versions." *Id.*, 11395.

Subsequent *in vitro* and *in vivo* testing confirmed Regeneron's hypotheses. VEGFTrap$_{R1R2}$ proved to be the best of all of the variants Regeneron created:

> The combination of high-affinity and improved pharmacokinetics apparently contributes toward making VEGF-Trap$_{R1R2}$ one of the most, if not the most, potent and efficacious VEGF blocker available.

> An additional advantage is that VEGF-Trap$_{R1R2}$ is composed of entirely human sequences, hopefully minimizing the possibility that it might prove immunogenic in human patients. Despite its wholly human nature, VEGF-Trap$_{R1R2}$ binds all species of VEGF tested, from human to chicken VEGF (not shown), making it a very versatile reagent that can be used in almost any experimental animal models.

Id., 11397. *Holash* also disclosed that the VEGF-Trap$_{R1R2}$ was created using CHO cells. *Id.*, 11394 ("All of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells.").

d. Wulff (EX1016)

Wulff is titled "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2" and was published in the scientific journal Endocrinology in July 2002, which is more than one year prior to the '992 patent's earliest possible priority date of June 2006 and thus *Wulff* qualifies as prior art under pre-AIA 35 U.S.C. 102(b) and post-AIA 35 U.S.C. 102(a)(1). *Wulff* lists Regeneron as an employer of at least one of the authors. EX1016, 2797.

Wulff conducted *in vivo* tests to investigate the ability of aflibercept to inhibit thecal angiogenesis in marmoset monkeys. *Id.*, 2798. *Wulff* noted 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 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 (Fig. 1)." *Id*. *Wulff* further noted that "[t]he VEGF trap was expressed in CHO cells and was purified by protein A affinity chromatography followed by size-exclusion chromatography. *Id.* *Wulff* refers the reader to the *'319 Publication* (EX1029) for the structure of VEGF-Trap$_{R1R2}$, stating that "the detailed molecular structure and how it was created are described in the patent REG 710-A-PCT, VEGF Trap Application published December 2000, Publication WO 00/75319 A1." *Id.*, n.1.

Wulff discloses the same formulation of aflibercept used in *Fraser*. It notes that "four marmosets were treated with VEGF trap at a dose of 25 mg/kg, injected sc on d 0, 2, 4, 6, and 8 of the follicular phase" and that "[c]ontrol animals were treated with vehicle containing 5mM phosphate, 5 mM citrate, 100 mM sodium chloride, 0.1% (wt/vol) Tween 20, and 20% (wt/vol) sucrose)." *Id.* 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. EX1002, ¶147.

e. '319 Publication (EX1029)

WO 00/75319 A1 ("*'319 Publication"*) is a PCT publication that was published on December 14, 2000, which is more than one year prior to the '992 patent's earliest possible priority date of June 2006 and thus qualifies as prior art under pre-AIA 35 U.S.C. 102(b) and post-AIA 35 U.S.C. 102(a)(1). It is entitled "Modified Chimeric Polypeptides with Improved Pharmacokinetic Properties" and states on its face that it is assigned to Regeneron. The *'319 Publication* is the "Publication WO 00/75319 A1" referred to in *Wulff* as disclosing the structure of VEGF-Trap$_{R1R2}$.

The *'319 Publication* describes its invention as "Flt1 receptor polypeptides that have been modified in such a way as to improve their pharmacokinetic profile," and as having "improved pharmacokinetic properties." *Id.,* 1:14-16; 10:3-4. It discloses the specific steps Regeneron took to develop aflibercept in more detail than in *Wulff*, including expression in CHO cells. *See id.*, Examples 17-21. It refers to aflibercept as VEGFR1R2-FcΔC1(a), which Regeneron has represented is another name for VEGF-Trap$_{R1R2}$. *Infra* subsection I.B.2.f. It also discloses the amino acid sequence and structure of VEGFR1R2-FcΔC1(a). EX1029, 11:14-12:1, 15:19-27, Fig. 24A-24C.

f. '309 Publication (EX1027)

U.S. Patent Application Publication No. 2004/0265309 (*'309 Publication*) is a U.S. patent publication that was published on December 30, 2004, which is more than one year prior to the '992 patent's earliest possible priority date of June 2006 and thus qualifies as prior art under pre-AIA 35 U.S.C. 102(b) and post-AIA 35 U.S.C. 102(a)(1). It is entitled "Method of Tumor Regression with VEGF Inhibitors" and states on its face that it was filed on behalf of Regeneron.

The *'309 Publication* discloses that VEGFR1R2-FcΔC1(a) is "also termed $VEGFTrap_{R1R2}$" and discloses its amino acid sequence. EX 1027, ¶5, SEQ ID NOs: 1 and 2. The *'309 Publication* also points the skilled artisan to the *'319 Publication* for "a complete description of VEGF-receptor based antagonists including VEGFR1R2-FcΔC1(a)" and incorporates the *'319 Publication* "by reference in its entirety." *Id.*, ¶22.

3. Level of Ordinary Skill in the Art

The 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. The POSA may also have had less education but substantially more practical relevant work experience. This individual 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. This individual also would have been able to use state-of-the-art analytical methods, such as SEC, to assess stability and compatibility. EX1002, ¶¶39-43.

This POSA also would have had access to other individuals typically employed in developing protein active pharmaceutical ingredients and products, including those involved in upstream and downstream manufacturing, analytical chemistry, pharmacokinetics, clinical testing, pharmaceutical packaging, and regulatory affairs. These diversely-qualified individuals would have worked together as needed during development. *Id.,* ¶¶42-43.

II. THE BOARD SHOULD DECLINE TO EXERCISE ITS DISCRETION TO DENY INSTITUTION

A. The Board Should Not Exercise Its Discretion Under Section 325(d) to Deny Institution

Patent Owner may urge the Board to deny institution because "the same or substantially the same prior art or arguments previously were presented to the Office," but the Board should decline to exercise its discretion to deny institution. 35 U.S.C. §325(d).

In determining whether to exercise its discretion to deny institution under §325(d), the Board applies a two-part framework. *Advanced Bionics, LLC v.*

MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 (Feb. 13, 2020) (precedential). The first part assesses "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." *Id.*, 8. "[I]f either condition of [the] first part of the framework is satisfied," the second part assesses "whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of [the] challenged claims." *Id.* The following factors help inform whether the first part of the framework is satisfied: "(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." *Id.*, 9-10; *see also Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (Dec. 15, 2017) (precedential).

This petition presents art and arguments that are materially different than those presented to the Office during prosecution of the ’992 patent. The only rejections made during prosecution of the application that led to the ’992 patent were obviousness-type double patenting rejections. EX1004, 76-79 (2019-04-02 Office Action). In order to avoid filing a terminal disclaimer, with the resulting loss of patent term, Regeneron amended the claims to recite the limitation relating to the of the protein conformation over time. *Id.*, 90-92. Regeneron then argued that none of the claims of Patent Nos. 8,092,803, 7,608,261, 9,340,594, and 9,914,763, nor application No. 15/879,294, included an element related to the added stability limitation. *Id.*, 93-94. Regeneron did not argue, however, that obtaining the added stability limitation was unexpected or that it conferred any unexpected properties to the formulation. Nor did Regeneron point the Examiner to *Dix*, which teaches the claimed stability limitation. *See, e.g.*, EX1021, Example 1, Tables 1 and 9.

The ’992 patent claims priority to a series of applications: U.S. Application Nos. 15/879,294, 15/095,606, 14/330,096, 13/914,996, 13/329,770, 12/833,417, 12/560,885, and 11/818,463. The 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. *See generally* EX1039-EX1046. The Examiner

did rely on a PCT publication (WO 2006/104,852) related to *Dix* (EX1021), relied on here, in making obviousness-type double patenting rejection (EX1039, 22-23; EX1043, 22-24), but Regeneron did not argue the merits of the rejection, but filed a terminal disclaimer to overcome the rejection (EX1039, 14-15; EX1043, 16-17). Nor was the *Dix* PCT publication cited when Regeneron added the stability limitation to the claims in the application leading to the '992 patent. At best, the Examiner noted that the closest prior art is Davis-Smyth (U.S. Patent No. 6,897,294) which the Examiner found did not "teach a chimeric receptor with less than all seven Ig-like domains that bind VEGF, or truncated fusion receptors with less than three Ig-Like domains that bind VEGF and thus does not anticipate or render obvious the claimed invention." EX1041, 14-15; EX1040, 7. Finally, *Fraser* was only cited in an IDS during the prosecution of the 15/879,924 and 15/095,606 applications. EX1045, 29; EX1046, 28.

Although *Fraser* was listed in an IDS in the application leading to the '992 patent and the 15/095,606 application, it was not cited or provided in an IDS in the earlier priority applications. Thus, 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.

And even if *Fraser* had been considered, Patent Owner did not make the Examiner aware of the *'319 Publication* or the *'309 Publication*, which disclosed that the VEGF $Trap_{R1R2}$ protein in the *Fraser* formulation is aflibercept, *i.e.*, the same VEGF antagonist comprising amino acids 27-457 of SEQ ID NO:4 that is described in the challenged claims. Nor did the Patent owner make the Examiner aware of *Wulff*, which used the same formulation as in *Fraser*, but also disclosed that Regeneron's VEGF $Trap_{R1R2}$ protein was made using CHO cells, as required by the challenged claims, and directed the reader to the *'319 Publication* and its disclosure that the VEGF $Trap_{R1R2}$ protein is aflibercept. Nor did the Patent Owner make the Examiner aware of *Dix*, which disclosed that Patent Owner's own tests established that the *Fraser* formulation met (and indeed exceeded) the 99% native conformation limitation of the challenged claims. This petition therefore 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.

A review of the *Becton Dickinson* factors support institution. As discussed, although *Fraser* was cited in an IDS, it was not involved during examination, and it was not similar to any prior art involved during prosecution, as the examiner did not make a prior art rejection in the application leading to the '992 application, nor in any of the applications to which the '992 application claims priority. Thus,

factor (a) supports institution. As no art rejections were made, *Fraser* is not cumulative to the prior art involved during examination, and as it was not the basis for any rejection, factors (b), (c), and (d) support institution. And since Petitioner has explained why failing to apply *Fraser* against the claims, including the failure of Regeneron to bring *Wulff*, the *'319 Publication*, the *'309 Publication*, or *Dix* to the attention of the Examiner, factors (e) and (f) support institution.

Moreover, through no fault of the examiner, the Office erred to any extent it evaluated *Fraser*. Patent Owner did not make the Examiner aware of *Wulff*, the *'319 Publication*, the *'309 Publication*, or *Dix*, which would have led the Examiner to conclude that the challenged claims were not patentable. Both parts of the Board's two-part framework are satisfied. The Board should thus decline to exercise its discretion under §325(d).

B. The Board Should Not Exercise Its Discretion under Section 314(a) to Deny Institution

Patent Owner may also urge the Board to exercise its discretion under §314(a) to deny institution because this is the second petition filed requesting IPR of claims 1-18 of the '992 patent. When evaluating whether to deny institution of a "follow-on" petition, the Board generally looks to seven factors: (1) whether the same petitioner previously filed a petition directed to the same claims of the same patent; (2) whether at the time of filing of the first petition the petitioner knew of the prior art asserted in the second petition or should have known of it; (3) whether

at the time of filing of the second petition the petitioner already received the patent owner's preliminary response to the first petition or received the Board's decision on whether to institute review in the first petition; (4) the length of time that elapsed between the time the petitioner learned of the prior art asserted in the second petition and the filing of the second petition; (5) whether the petitioner provides adequate explanation for the time elapsed between the filings of multiple petitions directed to the same claims of the same patent; (6) the finite resources of the Board; and (7) the requirement under 35 U.S.C. § 316(a)(11) to issue a final determination not later than one year after the date on which the Director notices institution of review. *Gen. Plastic Indus. Co., Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19, 9-10 (Sept. 6, 2017) (precedential). As explained below, the *General Plastic* factors weigh heavily in favor of institution of the petition.

Factors (1) and (2) favor institution. This is the first petition filed by Celltrion against the '992 patent, and Celltrion was not a real-party-in-interest in the '0402 petition and has no connection whatsoever to the petitioner in the '0402 petition. Factor (3), (4), and (5) also favor institution. Celltrion had no say in the timing of the filing of the '0402 petition. Although this petition was filed after the patent owner preliminary response, this petition presents new prior art and arguments not raised in the '0402 petition and it is being filed before any

institution decision was made in the '0402 IPR. Patent Owner also cannot complain of any unfairness, since it consented to withdrawal of the petition after it filed its POPR and before the Board could issue a decision on institution.

Finally, factors (6) and (7) favor institution. Given the differences between the '0402 petition and the instant petition, the Board will not be using its resources to consider duplicative arguments. This is especially true as the '0402 petition was withdrawn before institution. And there is no reason that Petitioner is aware of that would prevent the Board from meeting its one-year statutory requirement to issue a final written decision after institution.

III. GROUNDS FOR STANDING (37 C.F.R. § 42.104(A))

Petitioner certifies that the '992 patent is available for IPR and that Petitioner is not barred or estopped from bringing this petition or challenging any claim of the '992 patent on the grounds identified herein. Petitioner has not filed a civil action challenging the validity of the '992 patent, nor has it been served with a complaint alleging infringement of the '992 patent. *See Motorola Mobility LLC v. Arnouse*, No. IPR2013-00010, 2013 WL 12349001, *3 (P.T.A.B. Jan. 30, 2013).

IV. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Pursuant to 37 C.F.R. §§ 42.8(a)(1) and 42.8(b), the following mandatory notices are provided as part of this Petition.

A. Real-Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

Celltrion, Inc., Celltrion Healthcare Co. Ltd. And Celltrion Healthcare U.S.A., Inc. are the real parties in interest.

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

The '992 patent was challenged in *Chengdu Kanghong Biotechnology Co., Ltd. v. Regeneron Pharmaceuticals, Inc.*, IPR2021-00402 (P.T.A.B.), which the parties voluntarily terminated on June 25, 2021. The '992 patent is currently the subject of an *ex parte* reexamination, Control No. 90/014,448, wherein the requestor challenges the claims on obviousness-type double-patenting. While the reexamination was ordered, no substantive action has been taken. The '992 patent is currently being asserted in *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, Case No. 1-22-cv-00061 (N.D.W.V), filed on August 2, 2022. To the best of Petitioner's knowledge, there are no other judicial or administrative matters that would affect, or be affected by, a decision in this proceeding.

C. Lead and Back-Up Counsel and Service Information (37 C.F.R. § 42.8(b)(3), (4))

Lead counsel is Lora M. Green (Reg. No. 43,541). Back-up counsel are Robert Cerwinski (to be admitted *pro hac vice*), Aviv Zalcenstein (to be admitted *pro hac vice*), David Kim (to be admitted *pro hac vice*) and Brigid Morris (to be admitted *pro hac vice*).

Petitioner hereby consents to electronic service. Please direct all correspondence to lead and back-up counsel at the contact information below. A power of attorney accompanies this petition.

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D. Payment of Fees Under 37 C.F.R. § 42.15(a) and § 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

V. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

A. Challenged Claims and Relief Requested

Petitioner requests IPR of claims 1-18 of the '992 patent and cancellation of these claims as unpatentable.

B. Statutory Grounds of Challenge

Each of the following prior art references and/or combinations of references renders the challenged claims unpatentable:

Ground	Claims	References
1	1-18	Anticipated by *Fraser* (EX1009)
2	1-18	Obvious over the combination of *Fraser*, *Wulff* (EX1016), and *Holash* (EX1010), in light of the *'319 Publication* (EX1029), the *'309 Publication* (EX1027) *McNally 2000* (EX1013) and *FDA Container Closure Guidance* (EX1038)

Petitioner's full statement of the reasons for the relief requested is set forth in greater detail below, as supported by the declaration of Dr. Tarantino (EX1002).

VI. CLAIM CONSTRUCTION

The claim terms should be given their ordinary and customary meaning consistent with the specification, as a POSA would have understood them. 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*). Petitioner provides claim constructions for three terms, none of which are defined in the patent, and all of which should be given their plain and ordinary meaning to a POSA. EX1002, ¶¶19-21.

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. As explained by Dr. Tarantino, while the patent claims refer to the percentage of protein in "native conformation following storage at 5 °C for two months *as measured by size exclusion chromatography*," this usage presents a minor technical inconsistency. Protein in native conformation may co-elute with other substances, including degraded protein, that has a similar size, molecular weight or shape as the natively-conformed protein and thus migrates with it on the size-exclusion column being used. EX1002, ¶22.

The POSA would have understood the term "vial" in claims 1-9 to refer to a small closed or closable vessel, especially for liquids. EX1031; EX1002, ¶¶23, 190.

The 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. EX1002, ¶24.

VII. GROUNDS FOR UNPATENTABILITY – DETAILED ANALYSIS

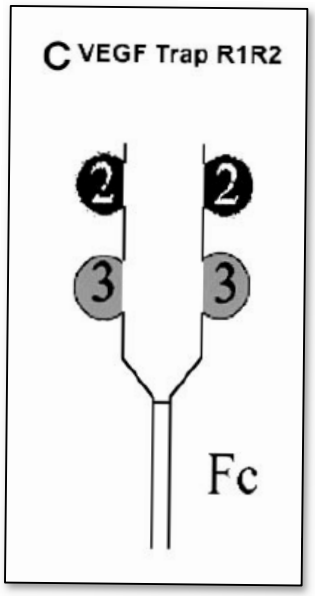
A. Ground 1: Claims 1-18 are Anticipated by *Fraser*

1. Claim 10

Claim 10 covers a formulation comprising any amount of a vascular endothelial growth factor (VEGF) antagonist, an unspecified organic co-solvent in

an unspecified amount, an unspecified buffer in an unspecified amount, and an unspecified stabilizing agent in an unspecified amount, wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell. The fusion protein comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component. At least 98% of the VEGF antagonist must be present in native conformation following storage at 5° C for two months as measured by SEC. Every element of claim 10 is disclosed in *Fraser*. EX1002, ¶88.

Fraser discloses a formulation of "$VEGFTrap_{R1R2}$." EX1009, 1115; EX1002, ¶90. $VEGFTrap_{R1R2}$ is a "VEGF antagonist" that "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" as required by claims 1 and 10. *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." EX1009, 1115. A "multimerizing component" refers to a component on an antibody or fusion protein that promotes multimerization, for example, joining two regions to form a dimer. EX1002, ¶24. As the diagram in Fig. 1 of *Wulff* illustrates, the human Fc portion of $VEGFTrap_{R1R2}$ acts as a "multimerizing component":



Id., ¶¶88-90.

A POSA would have understood that VEGFTrap$_{R1R2}$ is the same as VEGFR1R2-FcΔC1(a) and would have known its amino acid sequence. EX1016, n.1 (explaining that the *'319 Publication* describes the "detailed molecular structure" of VEGFTrap$_{R1R2}$); EX1029, 11:14-12:1, 15:19-27, Fig. 24A-24C (disclosing the amino acid sequence and structure of VEGFR1R2-FcΔC1(a); EX1027, ¶5, SEQ ID NOs: 1 and 2 (disclosing that VEGFR1R2-FcΔC1(a) is "also termed VEGF-Trap$_{R1R2}$ and disclosing the sequence of same); *see also* EX1002, ¶¶64-65, 95.

The *Fraser* formulation contains an "organic co-solvent, a buffer, and a stabilizing agent." *Fraser* states that "VEGFTrap$_{R1R2}$ (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." EX1009, 1115; EX1002 ¶91. Tween 20 is a brand name for polysorbate 20. EX1002, ¶73. Although *Fraser* states that the formulation contained either 20% glycerol or 20% sucrose, Regeneron's own notebooks indicate that the *Fraser* formulation contained 20% sucrose. EX1023, 2 (explaining that Exhibit C to EX1022 is a Regeneron notebook page disclosing "the actual lot and formulation used in Fraser"); EX1022, Exhibit C; EX1002, ¶¶91-92.

The VEGFTrap$_{R1R2}$ used in *Fraser* was produced in CHO cells and a POSA would have understood as much. *Fraser* notes that the VEGFTrap$_{R1R2}$ "was provided" by Regeneron, and references the *Holash* paper when describing its properties. EX1009, 1115. *Fraser* states: "Compared with earlier versions of receptor-based fusion proteins, the VEGFTrap$_{R1R2}$ exhibits greater affinity for VEGF-A (affinity constant ~1pM) as well as improved bioavailability and pharmacokinetic properties (21)." *Id*. Reference 21 is the *Holash* paper, which was authored by Regeneron scientists and published in 2002. *Holash* describes VEGF-Trap$_{R1R2}$ as follows: "VEGF-Trap$_{R1R2}$ was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells." EX1010, 11393-94. *Fraser*'s references to VEGFTrap$_{R1R2}$ being "provided" by Regeneron

and *Holash* as describing its properties would have informed a POSA that the $VEGFTrap_{R1R2}$ in *Fraser* was produced in CHO cells. *See also* EX1002, ¶¶93-95.

The POSA also would have been aware of *Wulff*, another Regeneron publication, which, like *Holash*, expressly disclosed that $VEGFTrap_{R1R2}$ was manufactured in CHO cells. EX1016, 2798. *Wulff* explains that $VEGFTrap_{R1R2}$ "was expressed in CHO cells and was purified by protein A affinity chromatography followed by size-exclusion chromatography." *Id.* *Wulff* also explains that Regeneron's *'319 Publication* (EX1029) describes "the detailed molecular structure" of $VEGFTrap_{R1R2}$ "and how it was created." EX1016, 2798, n.1. The *'319 Publication*, together with the *'309 Publication,* confirm that $VEGFTrap_{R1R2}$ was produced in CHO cells. EX1027, ¶26; EX1029, Example 21; EX1002, ¶¶93-95.

While *Fraser* does not disclose the percentage of aflibercept in the formulation that remained in native conformation after storage at 5 °C for two months, the stability of the *Fraser* formulation is the natural result of its ingredients. EX1002, ¶¶96-102. Merely testing the *Fraser* formulation to ascertain its stability does not make it patentable. *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."). The fact that the *Fraser*

formulation has the same ingredients as the claimed formulation is enough to establish a *prima facie* case of anticipation. *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977) (where a prior art composition is identical or substantially identical in structure or composition to a claimed one, a *prima facie* case of either anticipation or obviousness has been established with respect to claims directed to the properties of the claimed composition).

Regeneron cannot reasonably dispute that the claimed level of stability is the natural result of the ingredients in the *Fraser* formulation. Another Regeneron publication, *Dix*, published after the priority date, disclosed that Regeneron conducted stability testing on the same formulation[4] 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. EX1002, ¶¶96-102. *Dix* discloses a formulation

[4] In *Fraser*, the formulation contained 24.3 mg/ml of aflibercept. *Dix* states that the Table 9 formulation contained 25 mg/ml. A POSA would have understood that this is not a difference, since 24.3 mg/ml is within typical measurement error of 25 mg/ml. EX1002, ¶101. Even if it were not, formulations with higher concentrations of proteins like aflibercept tend to be less stable than those with lower concentrations. Thus, a skilled artisan would have understood that the embodiment in *Fraser* would have been *more* stable than the one in *Dix*. *Id.*, ¶102.

"containing about 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 25 mg/ml VEGF trap protein" with a "pH [that] ranged from 6.0-6.1." EX1021, 11:15-20. Table 9 of *Dix* shows that >99% of protein remained in native conformation in this formulation after storage for 2 months at 5 °C, as measured by SEC:

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

EX1021, 11:15-20-12:20, Table 9; EX1002, ¶¶97, 100. *Fraser* thus discloses every element of the formulation of claim 10 and anticipates it. EX1002, ¶103.

2. Claim 1

Claim 1 is drawn to the formulation of claim 10 placed in a "vial." The *Fraser* formulation was necessarily present in a "vial" and a POSA reading *Fraser* would have understood this. EX1002 ¶¶104-105. From *Fraser*, the POSA would have understood that Regeneron supplied to the clinicians a minimum of 14

"aliquots" of the anticipating $VEGFTrap_{R1R2}$ formulation, each containing 2 ml. EX1002, ¶105. Since the study was performed in macaque monkeys, an advanced primate species, and "approved by the local Primate Ethical Committee and carried out under a project license granted by the United Kingdom Office," EX1009, 1115, the POSA would have understood that Regeneron would have had to supply the 2 ml aliquots of study formulation in the same kind of specialized vials for injection used for human clinical trials, *i.e.*, sealed glass or plastic vials with a rubber stopper through which a needle could withdraw precise amounts of formulation. EX1002, ¶¶106-8. Standard good laboratory practice and ethical conventions would have required this in order to prevent contamination of the aliquots during use and storage, to ensure the well-being of the macaques, and to avoid compromising the study data.

Even if Regeneron did not supply the aliquots in vials for injection, they would necessarily have been supplied in vials of some kind. A POSA would have understood the claim term "vial" to have its plain meaning, *i.e.,* a small closed or closable vessel, especially for liquids. *See* EX1031; EX1002, ¶¶23, 109-11, 190. A POSA would have understood that Regeneron, at a minimum, would necessarily have had to supply the individual 2 ml aliquots in small, closed or closeable vessels in order to avoid contamination and spillage during transport and storage. EX1002, ¶¶105-106, 109. Indeed, Regeneron's own notebook shows that, prior to

supplying the aliquots used in *Fraser*, that same lot of formulation was stored in Regeneron's freezers in sealed tubes it described as "vials," to avoid just these sorts of hazards. *See* EX1023; EX1022, Exhibit C (showing that "Lot# VGFT01001T" was the "actual lot and formulation used in Fraser" and was stored in four "vials" at -80º C); EX1002, ¶¶110-13.

Claim 1 is thus also anticipated by *Fraser*. EX1002, ¶¶112-13.

3. Claims 2 and 11

Claims 2 and 11 depend from claims 1 and 10 respectively, and further require that "about 99% or more of the weight of the fusion protein" be "in native conformation." EX1001, 19:44-45, 20:41-43. As discussed, Regeneron's own SEC testing presented in Table 9 of *Dix* shows that the *Fraser* formulation exhibited >99% native conformation at 2 months. *Supra* Section VII(A)(1). This stability is an inherent property of Regeneron's prior-art formulation and does not distinguish claims 2 and 11 from *Fraser*. For these reasons and those explained above, *Fraser* anticipates claims 2 and 11. EX1002, ¶¶114-16.

4. Claims 3 and 12

Claims 3 and 12 depend from claims 1 and 10 respectively, and further require that "the first VEGF receptor" be "human Fltl" and "the second VEGF receptor" be "selected from the group consisting of human Flkl and the human Flt4." EX1001, 19:46-48, 20:44-47. VEGF-R1 is encoded by the Flt1 gene, while

VEGF-R2 is encoded by the Flk1 gene. *Supra* Section I(B)(1). The VEGF $Trap_{R1R2}$ in *Fraser* comprises "Ig domain 2 of human VEGF-R1 and Ig domain 3 of human VEGF-R2." EX1009, 1115. For these reasons and those explained above, *Fraser* anticipates claims 3 and 12. EX1002, ¶¶117-19.

5. Claims 4 and 13

Claims 4 and 13 depend from claims 3 and 12 respectively, and further require that "the fusion protein comprise[] amino acids 27-457 of SEQ ID NO: 4." EX1001, 19:51-52, 20:49-50. As the *'319 Publication* and *'309 Publication* show, the $VEGFTrap_{R1R2}$ used in *Fraser* has the amino acid sequence described in amino acids 27-457 of SEQ ID NO: 4. *Supra* Section I(B)(2). Further, a POSA would have known from these prior-art references that the sequence was inherent in *Fraser's* reference to "$VEGFTrap_{R1R2}$." *Id.*; EX1002, ¶¶65, 121-22. For these reasons and those explained in Sections VII(A)(1) and (3), *Fraser* anticipates claims 4 and 13. *Id.*, ¶¶120-23.

6. Claims 5 and 14

Claims 5 and 14 depend from claims 4 and 13 respectively, and further require that "the VEGF antagonist" be "a dimer of the fusion protein." EX1001, 19:51-52, 20:51-52. As discussed, *Wulff*, the *'319 Publication* and *'309 Publication* show that the $VEGFTrap_{R1R2}$ used in *Fraser* is a dimer. *Supra* Section VII(A)(1). A POSA would have known from these prior-art references that the

claimed structure was inherent in *Fraser's* reference to "$VEGFTrap_{R1R2}$." EX1002, ¶57. For these reasons and those explained in Sections VII(A)(1) and (4), *Fraser* anticipates claims 5 and 14. *Id.*, ¶¶124-26.

7. Claims 6 and 15

Claims 6 and 15 depend from claims 5 and 14 respectively, and further require that "the organic co-solvent" be "selected from the group consisting of polysorbate 20, polysorbate 80, polyethylene glycol (PEG), PEG3350, and propylene glycol." EX1001, 19:53-56, 20:51-52. As discussed, the *Fraser* formulation contains "0.1% wt/ vol Tween 20." EX1009, 1115. "Tween 20" is a trade name for polysorbate 20. EX1002, ¶73. For these reasons and those explained in Sections VII(A)(1) and (5), *Fraser* anticipates claims 6 and 15. *Id.*, ¶¶127-29.

8. Claims 7 and 16

Claims 7 and 16 depend from claims 6 and 15 respectively, and further require that "the stabilizing agent" be "selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol." EX1001, 19:57-59, 20:57-59. As discussed, *Fraser* states that the formulations used contained "either 20% glycerol or 20% sucrose." EX1009, 1115. As explained, Regeneron represented to the Office that *Fraser's* formulation actually contained 20% sucrose. *Supra*

Section VII(A)(1), (6). For these reasons and those explained above, *Fraser* anticipates claims 7 and 16. EX1002, ¶¶130-32.

9. Claims 8 and 17

Claims 8 and 17 depend from claims 1 and 10 respectively, and further requires that "the organic co-solvent" be "polysorbate 20" and "the stabilizing agent" be "sucrose." EX1001, 19:60-61, 20:59-61. As discussed, the *Fraser* formulation contains 20% sucrose and 0.1% polysorbate 20. *Supra* Section VII(A)(1). For these reasons and those explained in Section VII(A)(1), *Fraser* anticipates claims 8 and 17. EX1002, ¶¶133-35.

10. Claims 9 and 18

Claims 9 and 18 depend from claims 1 and 10 respectively, and further recite "the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose." EX1001, 19:62-64, 20:63-65. As discussed, the *Fraser* formulation contained 5 mM phosphate, 20% sucrose, and 0.1% polysorbate 20. *Supra* Section VII(A)(1). For these reasons and those explained above, *Fraser* anticipates claims 9 and 18. EX1002, ¶¶136-38.

B. Claims 1-18 are Obvious Over the Combination of *Fraser*, *Holash*, and *Wulff*, in view of the *'319 Publication*, the *'309 Publication*, *McNally 2000*, and *FDA Container Closure Guidance*

Even if *Fraser* does not expressly or inherently disclose all limitations of the formulation of the challenged claims, which it does, *Fraser* would have rendered

those limitations trivially obvious to the POSA in view of *Holash*, *Wulff,* the *'319 Publication* and the *'309 Publication*, alone or in combination with *McNally 2000*'s guide on optimizing stability. EX1002, ¶53. Placing that formulation in a "vial" would have required nothing more than a POSA's common knowledge and sense, but also would have been obvious from *FDA Container Closure Guidance*. EX1002, ¶139.

1. Claims 1 and 10

a) A POSA would have been motivated to formulate aflibercept since it was known to have great therapeutic promise

As discussed in Section VII(A), claims 1 and 10 require a formulation comprising a vascular endothelial growth factor (VEGF) antagonist, 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. As explained, Regeneron's aflibercept was well-documented in the prior art and known to meet these limitations. EX1002, ¶140. The prior art would have given a POSA ample motivation for making a formulation of this particular VEGF inhibitor.

As the '992 patent acknowledges, it was well known in the field that VEGF inhibitors were useful in the treatment of cancer and other diseases in which

angiogenesis plays a role. EX1001, 1:41-52. Regeneron had published multiple *in vitro* and *in vivo* studies demonstrating that aflibercept—VEGFTrap$_{R1R2}$—had the best *in vivo* pharmacokinetics and anti-VEGF activity of all of the VEGF-trap proteins Regeneron had been studying. EX1009; EX1010; EX1016; *see also* EX1029, 10 (describing VEGFTrap$_{R1R2}$ as having "improved pharmacokinetic properties"); EX1002, ¶¶140-42.

Further, aflibercept compared favorably to other non-Regeneron VEGF antagonist human therapeutics that had been approved by FDA, such as monoclonal antibodies like bevacizumab and ranibizumab. As Regeneron's scientists put it, "[t]he combination of high-affinity and improved pharmacokinetics apparently contributes toward making VEGF-Trap$_{R1R2}$ [aflibercept] one of the most, if not the most, potent and efficacious VEGF blocker available." EX1010, 11397; EX1002, ¶142.

In these same publications, Regeneron noted that aflibercept had the additional advantage of being composed of "entirely human sequences," which would "hopefully minimize the possibility that it might prove immunogenic in human patients." *Id.* Further, in comparison to existing antibody VEGF antagonists, "far lower circulating levels of VEGF-Trap$_{R1R2}$ [aflibercept] are required for similar efficacy" and its "safety has recently been confirmed in toxicological studies in cynomologus monkeys." *Id.*

As a result of these superior properties, Regeneron disclosed that "the [aflibercept] VEGF-Trap is currently in human clinical trials for several different types of cancer." *Id.* By 2005-06, Regeneron had published positive *in vivo* data for aflibercept in at least some of these initial human clinical trials in human patients. EX1015, 414-15. From these Regeneron publications, a POSA would have been motivated to make formulations of aflibercept that were sufficiently stable to be approved as a therapeutic product in humans and animals. EX1002, ¶¶140-42.

The same Regeneron prior art also would have motivated a POSA to make the aflibercept in CHO cells. Regeneron had published that it had produced its $VEGFTrap_{R1R2}$ using CHO cells. *See* EX1016, 2798 (disclosing $VEGFTrap_{R1R2}$ and that "the VEGF Trap was expressed in CHO cells"); EX1010, 11393-94 (disclosing $VEGFTrap_{R1R2}$ and that "[a]ll of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells."). A POSA seeking to reproduce the performance of aflibercept that Regeneron observed would also have used CHO cells, since (1) that's what Regeneron did and there would have been no reason to choose a different mammalian cell type; (2) expression in a different mammalian cell type carried at least some risk that post-translational processing of the aflibercept might be different than in CHO cells, which could change the protein's performance, and (3) expression in a different mammalian cell type

carried at least some risk of producing additional host cell protein and/or DNA impurities, and would wish to avoid this risk as much as possible by sticking to a proven method that was already shown to have worked (*i.e.*, cultivation in CHO cells). EX1002, ¶¶143-45, 189; EX1047, 12 (FDA Guidance instructing formulators to minimize impurities such as host cell protein and/or DNA impurities); EX1017, 1396 ("CHO cells now dominate the domain of mass production of recombinant protein products because of their capacity for single-cell suspension growth.").

b) A POSA would have been motivated to place the formulation in a vial

The POSA also would have had ample motivation to use a "vial" to contain the aflibercept formulation, as required by claim 1. EX1002, ¶¶161-64. Common sense alone would have dictated that doses of the formulation be kept in a vial—a small closed or closable vessel, especially for liquids, to avoid contamination and spillage. EX1002, ¶162. Further, aflibercept is typically administered via injection, s*ee, e.g.,* EX1009, 1115; EX1016, 2798; EX1010, 11396, and as explained, injectable therapeutic protein formulations are most often provided in vials for injection. This is to, *e.g.,* adhere to good laboratory practice, preserve the integrity of the formulation during use and storage, and aid administration. *Supra* Section VII(A)(2); EX1002, ¶¶161-62. Such vials are also by far the most practical means to store solid lyophilized protein formulations for reconstitution

prior to injection; they could also be coated or made of materials to minimize interaction of the protein with the container. *Id.* In fact, in *FDA Container Closure Guidance*, published in 1999, FDA specifically recommended that injectable formulations be packaged in vials. EX1038, 23-24, n.19. EX1002, ¶¶162-63, 189.

c) The only published aflibercept formulation for in vivo *use contained the claimed excipients*

The prior art also would have motivated a POSA to select an organic co-solvent, a buffer, and a stabilizing agent as excipients for a stable formulation of aflibercept, as required by claims 1 and 10. As explained, in *Fraser* and *Wulff*, Regeneron published the fact 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. EX1009, 1115; EX1016, 2798; EX1002, ¶¶146-47. A POSA would have paid particular attention to the composition of a formulation used by the innovator of a new biologic, since they would have presumed that the innovator was the most familiar with the biologic's physical and chemical characteristics. EX1002, ¶147. Indeed, this was the *only* formulation of aflibercept that was published for *in vivo* use, which would have left the POSA with only one clear starting point when making a formulation for such use. *Id.*

Regeneron also published that this formulation sufficiently stabilized the aflibercept so that it remained useable over a two-week period when stored at 4º C.

EX1009, 1115. This substantial stability would have led a POSA to select the Regeneron's proven formulation as a starting point rather than try to devise an entirely new formulation from scratch. EX1002, ¶¶148-50. Capitalizing on this starting point would have enabled the POSA to avoid much if not all of the trial-and-error process of selecting and testing various combinations of commonly-used excipients to determine which were optimal for aflibercept. EX1002, ¶150.

d) The claimed level of stability does not distinguish the claimed formulation from the prior art

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 also would have been obvious.

As a preliminary matter, the '992 patent does not describe this storage stability as being critical to the allegedly inventive formulation. This limitation appears to only be the product of simply claiming the test results reported in the examples of the '992 patent, all of which contained aflibercept, polysorbate 20, phosphate buffer and sucrose or glycerol. *See supra* Section I(A).

As explained in Sections V(I)(B)(1)(b) and 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. *Best*, 562 F.2d at 1255.

Further, a POSA would have been motivated to use the *Fraser* formulation make a commercial aflibercept product that was as stable as possible. The more stable a formulation is, the longer its "shelf life" or period between manufacture and expiry. EX1002, ¶¶81, 151-53. All FDA-approved medications have an approved shelf life that dictates a product's expiration date, beyond which the product cannot be sold or dispensed in the U.S. A POSA would have regarded a formulation of aflibercept with a longer shelf life to be more desirable than one with a shorter shelf life because a manufacturer and its customers, including pharmacies, healthcare providers and patients, would end up discarding fewer doses due to product expiration. EX1002, ¶153.

A POSA also would have been motivated to reduce aggregation as much as possible. As explained, aggregates can cause undesirable immunogenicity. Aggregates of all sizes can reduce the quality and potency of a biologic product. EX1002, ¶¶72-74, 154. Accordingly, a POSA would have been motivated to reduce aggregates of all sizes as much as possible. *Id*.

SEC tests that measure the formation of aggregates and other impurities by after storage for two months at 5º C were among the most common in the pharmaceutical industry as of 2006. When assessing aggregate formation in the aflibercept formulation, a POSA would have viewed these test conditions as being both routine and generally accepted among formulators. EX1002, ¶¶79, 151.

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. EX1002, ¶153.

A POSA would have readily achieved this goal by simply doing the obvious thing and copying the *Fraser* formulation. As explained, the POSA would have started with Regeneron's formulation disclosed in *Fraser* and *Wulff,* which sufficiently stabilized the aflibercept to make it useable after two weeks when stored at 5º C. The POSA would then have engaged in routine SEC stability testing and, as *Dix* shows, would have found that this formulation met and exceeded the 99% threshold after storage for two months at 5º C. EX1002, ¶¶150-51.

Even if the POSA initially achieved a lower level of stability, the POSA would reasonably have expected to be able to optimize the formulation to achieve the claimed level of natively-conformed protein. As of 2006, formulators possessed a relatively high degree of skill in stabilizing protein therapeutics. Using the Regeneron formulation disclosed in *Fraser* and *Wulff* as a starting point, 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. EX1002, ¶¶153-59. To reduce

aggregation over time, the POSA would have focused in particular on the concentration of polysorbate 20 and pH, for the reasons set forth in Section I(B)(1)(c). *Id.* While this might have required a series of experiments designed to determine the optimal value for each of these variables, the design and execution of such experiments would have been routine and well within ordinary skill. EX1002, ¶¶156-59. And as *McNally 2000* shows, if a POSA needed a guide as to how to design such experiments, "step-by-step, how-to" protocols to "enable the formulation scientist to proceed through a protein solution formulation development study" were readily available. EX1013, 156, 157 (teaching detailed three-step protocol that sets forth the "natural sequence to the order in which individual [formulation] parameters are investigated" and how to investigate them). 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. *See E.I. Dupont de Nemours v. Synvina C.V.,* 904 F.3d 996, 1006 (Fed. Cir. 2018).

Indeed, the '992 patent assumes that such optimization is well within the capability of an ordinary formulator. The patent broadly claims formulations containing *any* amount of a *wide variety* of VEGF antagonist proteins, organic co-solvents, buffers and stabilizers, but only discloses a relative handful of specific embodiments in the examples, each of which contain polysorbate 20 or

polyethylene glycol 3350, phosphate buffer and sucrose. The patent assumes a POSA can adjust the specific amounts of these ingredients—and a broad range of others that fall within the claims—in order to achieve the claimed level of stability. *Supra* Section I.A. Since Regeneron had already disclosed its aflibercept formulation containing polysorbate 20, phosphate-containing buffer and sucrose, all a POSA would have had to do to arrive at the claimed invention would be to apply the very same routine adjustments required by the '992 patent to the prior art. This is not inventive. EX1002, ¶159. For the foregoing reasons, claims 1 and 10 are obvious. EX1002, ¶¶160, 164.

2. Claims 2 and 11

Claims 2 and 11 depend from claims 1 and 10, respectively and further specify that "about 99% or more of the weight of the fusion protein" be "in native conformation." For all of the reasons discussed in Section VII(B)(1) above with respect to claims 1 and 10 regarding the obviousness of the 98% stability limitation, this 99% stability limitation does not render claims 2 and 11 patentable. Claims 2 and 11 are thus obvious for the same reasons as claims 1 and 11. EX1002, ¶¶165-67.

3. Claims 3 and 12

Claims 3 and 12 depend from claims 1 and 10 respectively, and further require that "the first VEGF receptor" be "human Fltl" and "the second VEGF

receptor" be "selected from the group consisting of human Flkl and the human Flt4." EX1001, 19:46-48, 20:44-47. Per Section I(B)(1), VEGF-R1 is encoded by the Flt1 gene, while VEGF-R2 is encoded by the Flk1 gene. *Fraser* disclosed that aflibercept (VEGF $Trap_{R1R2}$) comprises "Ig domain 2 of human VEGF-R1 and Ig domain 3 of human VEGF-R2." EX1009, 1115. Therefore, the additional limitations of claims 3 and 12 do not render them patentable and they are obvious for the same reasons as explained for claims 1 and 10. EX1002, ¶¶168-69.

4. Claims 4 and 13

Claims 4 and 13 depend from claims 3 and 12 respectively, and further require that "the fusion protein comprise[] amino acids 27-457 of SEQ ID NO: 4." EX1001, 19:51-52, 20:49-50. Per Section I(B)(2), a POSA would have known from the *'319 Publication* and *'309 Publication* that the $VEGFTrap_{R1R2}$ used in *Fraser* has the amino acid sequence described in amino acids 27-457 of SEQ ID NO: 4. This additional limitation does not make claims 4 and 13 patentable. They are obvious for the same reasons as explained for claims 1 and 10. EX1002, ¶¶170-72.

5. Claims 5 and 14

Claims 5 and 14 depend from claims 4 and 13 respectively, and further require that "the VEGF antagonist" be "a dimer of the fusion protein." EX1001, 19:51-52, 20:51-52. Per Section VII(A)(1), a POSA would have understood that

the $VEGFTrap_{R1R2}$ used in *Fraser* is a dimer, thus this additional limitation does not make claims 5 and 14 patentable. They are obvious for the same reasons as claims 1 and 10. EX1002, ¶¶173-74.

6. Claims 6 and 15

Claims 6 and 15 depend from claims 5 and 14 respectively, and further require that "the organic co-solvent" be "selected from the group consisting of polysorbate 20, polysorbate 90, polyethylene glycol (PEG), PEG3350, and propylene glycol." EX1001, EX1001, 19:53-56, 20:51-52. Per Section VII(A)(1), the *Fraser* formulation contains "0.1% wt/ vol Tween 20." EX1009, 1115. "Tween 20" is a trade name for polysorbate 20. EX1002, ¶73. Accordingly, this additional limitation does not make claims 5 and 14 patentable. They are obvious for the same reasons as claims 1 and 10. *Id*., ¶¶175-76.

7. Claims 7 and 16

Claims 7 and 16 depend from claims 6 and 15 respectively, and further require that "the stabilizing agent" be "selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol." EX1001, 19:57-59, 20:57-59. Per Section VII(A)(1), the *Fraser* formulation contained 20% sucrose. Moreover, even if this limitation is not inherent in *Fraser*, *Fraser* discloses a formulation containing "either 20% glycerol or 20% sucrose." EX1009, 1115. Even if the POSA did not select 20% sucrose first, the POSA would have selected and tested

both 20% sucrose and 20% glycerol. Selecting two slightly different prior-art Regeneron formulations to proceed with does not rise to the level of undue experimentation. Accordingly, this additional limitation does not make claims 7 and 16 patentable. They are obvious for the same reasons as claims 1 and 10. EX1002, ¶¶177-80.

8. Claims 8, 9, 17, and 18

Claims 8 and 17 depend from claims 1 and 10 respectively, and further requires that "the organic co-solvent" be "polysorbate 20" and "the stabilizing agent" be "sucrose." EX1001, 19:60-61, 20:59-61. Claims 9 and 18 depend from claims 1 and 10 respectively, and further recite "the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose." EX1001, 19:62-64, 20:63-65. Per Section VII(A)(1), *Fraser* discloses a formulation containing phosphate buffer, polysorbate 20 and "either 20% glycerol or 20% sucrose." EX1009, 1115. *Wulff* discloses the same formulation containing phosphate buffer, polysorbate 20 and 20% sucrose. EX1016, 2798. A POSA would have been motivated to start with the sucrose-containing formulation that Regeneron itself had published in *Fraser* and *Wulff*. EX1002, ¶183. Even if a POSA did not select 20% sucrose first, a POSA would have selected and tested both 20% sucrose and 20% glycerol. Selecting two slightly different prior-art Regeneron formulations to proceed with does not rise to the level of undue

experimentation. Accordingly, these additional limitations do not make claims 8, 9, 17, and 19 patentable. They are obvious for the same reasons as claims 1 and 10. EX1002, ¶¶181-85.

9. Secondary Evidence of Non-Obviousness

Petitioner is not aware of any relevant secondary considerations that have a nexus to, or are commensurate in scope, with any of the challenged claims. EX1002, ¶186. Petitioners reserves the right to respond to any allegations of secondary considerations.

VIII. CONCLUSION

For the reasons set forth above, claims 1-18 of the '992 patent are unpatentable. Petitioners therefore request that a *inter partes* review of these claims be instituted and that the claims be cancelled.

Respectfully submitted,

Dated: January 17, 2023

/ Lora M. Green /
Lora M. Green, Lead Counsel
Reg. No. 43,541

IX. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,931 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: January 17, 2023

/ Lora M. Green /
Lora M. Green, Lead Counsel
Reg. No. 43,541

X. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 10,464,992 ("*'992 patent*")
1002	Declaration of Dr. Ralph Tarantino ("*Tarantino*")
1003	Dr. Ralph Tarantino *curriculum vitae*
1004	File History of U.S. Application No. 16/159,269 ("*'992 Prosecution History*")
1005	James D. Andya et al., *Mechanisms of Aggregate Formation and Carbohydrate Excipient Stabilization of Lyophilized Humanized Monoclonal Antibody Formulations*, 5(2) AAPS PHARMSCI (Apr. 4, 2003) ("*Andya 2003*")
1006	Byeong S. Chang & Susan Hershenson, *Practical Approaches to Protein Formulation Development* in RATIONALE DESIGN OF STABLE PROTEIN FORMULATIONS – THEORY AND PRACTICE, 1-25 (J.F. Carpenter and M.C. Manning eds., 2002) ("*Chang 2002*")
1007	Eva Y. Chi et al., *Physical Stability of Proteins in Aqueous Solution: Mechanism and Driving Forces in Nonnative Protein Aggregation*, 20 PHARMACEUTICAL RESEARCH 9, 1325-1336 (Sept. 2003) ("*Chi*")
1008	Napoleone Ferrara & Robert S. Kerbel, *Angiogenesis as a Therapeutic Target*, 438 NATURE 967-74 (Dec. 15, 2005) ("*Ferrara 2005*")
1009	Hamish M. Fraser et al., *Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function*, 90(2) J. CLIN. ENDOCRINOL. & METAB. 1114-1122 (Feb. 2005) ("*Fraser*")
1010	Jocelyn Holash et al., *VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects*, 99 (17) PNAS 11393-11398 (Aug. 20, 2002) ("*Holash*")
1011	Janeway et al., *The Structure of a Typical Antibody Molecule* in IMMUNOBIOLOGY: THE IMMUNE SYSTEM IN HEALTH AND DISEASE, 5th ed., 94-100 (2001) ("*Janeway*")

1012	Leopold K. Kostanski et al., *Size-exclusion Chromatography – a Review of Calibration Methodologies*, 58 J. BIOCHEM. BIOPHYS. METHODS 159-186 (2004) ("*Kostanski 2004*")
1013	Paul McGoff & David S. Scher., *Solution Formulation of Proteins/Peptides* in PROTEIN FORMULATION AND DELIVERY vol. 99, 139-58 (2000) ("*McNally 2000*")
1014	Dave A. Parkins & Ulla T. Lashmar, *The Formulation of Biopharmaceutical Products,* 3(4) PHARM. SCI. & TECH. TODAY 129-137 (Apr. 4, 2000) ("*Parkins*")
1015	J.S. Rudge et al., *VEGF Trap as a Novel Antiangiogenic Treatment Currently in Clinical Trials for Cancer and Eye Diseases, and VelociGene®-based Discovery of the Next Generation of Angiogenesis Targets*, 70 COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY 411-418 (2005) ("*Rudge*")
1016	Christine Wulff et al., *Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2*, 143(7) ENDOCRINOLOGY 2797-2807 (Jul. 2002) ("*Wulff*")
1017	Florian M. Wurm, *Production of Recombinant Protein Therapeutics in Cultivated Mammalian Cells*, 22 NATURE BIOTECHNOLOGY 1393-1398 (Nov. 2004) ("*Wurm*")
1018	U.S. Patent No. 6,171,586 to Lam et al. ("*'586 Patent*")
1019	U.S. Patent No. 7,374,758 to Papadopoulos et al. ("*'758 Patent*")
1020	Application for Extension of Patent Term to U.S. Patent No. 7,374,758 ("*'758 PTE*")
1021	U.S. Patent No. 8,110,546 to Dix et al. ("*Dix*")
1022	Declaration Pursuant to 37 C.F.R. § 1.131 of Daniel B. Dix, Kelly Frye, and Susan Kautz in Support of U.S. Application No. 12/835,065 ("*Declaration of Dix et al.*")
1023	Response to Office Action of July 13, 2011 in U.S. Application No. 12/835,065 ("*Nov 22 OA Response*")
1024	U.S. Patent Publication No. 2003/0113316 to Kaisheva et al. ("*Kaisheva '316*")

1025	U.S. Patent Publication No. 2003/0138417 to Kaisheva et al. ("*Kaisheva '417*")
1026	U.S. Patent Publication No. 2004/0197324 to Liu et al. ("*Liu*")
1027	U.S. Patent Publication No. 2004/0265309 to Kandel et al. ("*'309 Publication*")
1028	U.S. Patent Publication No. 2005/0112061 to Holash et al. ("*'061 Publication*")
1029	International Publication No. WO 00/75319 to Papadopoulos et al. ("*'319 Publication*")
1030	International Publication No. WO 97/04801 to Andya et al. ("*WO '801*")
1031	*Vial*, Merriam-Webster.com, https://merriam-webster.com/dictionary/vial (last visited Jan. 16, 2023) ("*Merriam Webster Vial Definition"*)
1032	AVASTIN®, *Approved Labeling*, CENTER FOR DRUG EVALUATION AND RESEARCH (2004) ("*AVASTIN Label*")
1033	RAPTIVA®, *Physicians' Desk Reference* (59th ed. 2005) ("*RAPTIVA Label*")
1034	REMICADE®, *Physicians' Desk Reference* (59th ed. 2005) ("*REMICADE Label*")
1035	SIMULECT®, *Physicians' Desk Reference* (59th ed. 2005) ("*SIMULECT Label*")
1036	HERCEPTIN®, *Physicians' Desk Reference* (59th ed. 2005) ("*HERCEPTIN Label*")
1037	XOLAIR® label, *Physicians' Desk Reference* (59th ed. 2005) ("*XOLAIR Label*")
1038	Food & Drug Administration, *Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999) ("*FDA Container Closure Guidance*")
1039	Excerpts from Prosecution History of U.S. Application No. 11/818,463 ("*'463 Excerpts*")
1040	Excerpts from Prosecution History of U.S. Application No. 12/560,885 ("*'885 Excerpts*")

1041	Excerpts from Prosecution History of U.S. Application No. 12/833,417 ("*'417 Excerpts*")
1042	Excerpts from Prosecution History of U.S. Application No. 13/329,770 ("*'770 Excerpts*")
1043	Excerpts from Prosecution History of U.S. Application No. 13/914,996 ("*'996 Excerpts*")
1044	Excerpts from Prosecution History of U.S. Application No. 14/330,096 ("*'096 Excerpts*")
1045	Excerpts from Prosecution History of U.S. Application No. 15/095,606 ("*'606 Excerpts*")
1046	Excerpts from Prosecution History of U.S. Application No. 15/879,294 ("*'294 Excerpts*")
1047	U.S. Department of Health and Human Services, Food & Drug Administration, Guidance for Industry, *Guidance for Industry* (Aug. 1999) ("*FDA Specification Guidance*")

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for Inter Partes Review (and accompanying Exhibits 1001-1047) by overnight courier (Federal Express or UPS), on this 17th day of January, 2023, on the Patent Owner at the correspondence address of the Patent Owner as follows:

A&P – Regeneron
Attn: IP Docketing
601 Massachusetts Avenue, N.W.
Washington, DC 20001

Respectfully submitted,

Dated: January 17, 2023

/ Lora M. Green /
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