UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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CHENGDU KANGHONG BIOTECHNOLOGY CO., LTD.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Patent No. 10,464,992
Issue Date: November 5, 2019
Title: VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

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Inter Partes Review No. IPR2021-00402

PETITION FOR *INTER PARTES* REVIEW

UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 *et seq.*

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Petitioner Chengdu Kanghong Biotechnology Co., Ltd. ("Petitioner" or "Kanghong") respectfully petitions for *inter partes* review in accordance with 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100 *et seq*. of all claims of U.S. Patent No. 10,464,992 ("the '992 patent" (Ex. 1001)), which issued on November 5, 2019 and is purportedly assigned to Regeneron Pharmaceuticals, Inc. ("Patent Owner" or "Regeneron"). This Petition demonstrates that all claims are unpatentable.

I. INTRODUCTION

The '992 patent claims known a vascular endothelial growth factor ("VEGF") antagonist in a formulation with excipients (organic co-solvent, a buffer, and a stabilizing agent) that were also well-known. The purportedly novel feature of the invention is a percentage of VEGF antagonist that remains after storage.

Many times before the '992 patent's earliest priority date (June 16, 2006), Patent Owner disclosed formulations with claim 1's VEGF antagonist and excipients. In 2005, Fraser et al. published the claimed VEGF antagonist and excipients. (Ex. 1004.) Although Fraser does not disclose its stability, Regeneron elsewhere described the Fraser formulation as including the claimed percentage of VEGF antagonist after storage. Thus, the Fraser formulation, as evidenced by Patent Owner's admissions, inherently anticipates and/or renders obvious the '992 patent.

Earlier, in a 2002 article by Wulff et al., Regeneron disclosed a VEGF antagonist formulation with the same excipients and the same percentages as Fraser. Although Wulff does not disclose the stability property of its formulation, it was routine in the art to optimize stability of formulations by adjusting excipient concentrations. Thus, Wulff renders obvious the claims of the '992 patent.

These published formulations, either alone or in combination with other references, invalidate all claims of the '992 patent under 35 U.S.C. § 102 and/or § 103[1].

Petitioner submits that this Petition demonstrates a reasonable likelihood that Petitioner will prevail on at least one challenged claim, requests institution of *inter partes* review of the '992 patent, and requests the Board find that all claims of the '992 patent are invalid.

II. THE '992 PATENT

A. Background

The '992 patent is titled "VEGF Antagonist Formulations Suitable For Intravitreal Administration." Despite the '992 patent's title, nothing in the claims

[1] The claims of the '992 patent are invalid under both pre-AIA and post-AIA 35 U.S.C. Unless stated otherwise, all references herein to 35 U.S.C. §§ 102 and 103 refer to both pre-AIA and post-AIA 35 U.S.C.

requires a formulation suitable for intravitreal administration. Independent claim 1 is representative:

> 1. A vial comprising:
> [1A] a vascular endothelial growth factor (VEGF) antagonist,
> [1B] an organic co-solvent, a buffer, and a stabilizing agent,
> [1C] wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell,
> [1D] 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
> [1E] wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.

(Ex. 1001 at 19:30-43.) Independent claim 10 is identical to claim 1, with the exception that the preamble recites "a formulation" (as opposed to claim 1's "a vial"). Dependent claims 2-9 and 11-18 further specify the percent of "native conformation" (claims 2 and 11), the VEGF receptors (claims 3 and 12), amino acid sequences of the fusion protein (claims 4 and 13), the VEGF antagonist (claims 5 and 14), the specific organic co-solvent, stabilizing agents, and buffer (claims 6-9, and 15-18).

The '992 patent states that VEGF is "nearly ubiquitous in human cancer, consistent with its role as a key mediator of tumor neoangiogenesis" and acknowledges that blockade of VEGF function was known to inhibit cancer growth since at least 2000. (Ex. 1001 at 1:41-47 (citations omitted).) The '992 patent

acknowledges that soluble VEGF-specific fusion protein antagonists (also known as "VEGF Traps") have been known since at least 2002. (*Id.* at 1:47-52.) The '992 patent lists Holash as teaching a VEGF-specific antagonist (*Id.* at 50-51 (citing Ex. 1007)); Holash's antagonist is the same VEGF trap cited in Fraser (discussed below in Grounds 1 and 2).

The '992 patent summarizes the invention as "[s]table formulations of a VEGF-specific fusion protein antagonist" (*Id.* at 1:66-67) and provides eight examples of such a formulation. These examples include anywhere from 20 to 50 mg/ml of a VEGF fusion protein antagonist with combinations of specific co-solvents, buffers, and stabilizing agents, each at a specific concentration for the respective example. (*Id.* at 8:8-12:20.)

The '992 claims are much broader. Where each of the eight examples in the '992 specification gives specific ingredients and concentrations of the ingredient, both independent claims 1 and 10 simply recite "an organic co-solvent, a buffer, and a stabilizing agent." Some dependent claims narrow the formulation to respective groups of organic co-solvents or stabilizing agents; some further claims narrow to a specific organic co-solvent, a specific buffer, and/or a specific stabilizing agent. But none of the '992 claims specifies a concentration of VEGF antagonist, organic co-solvent, buffer, and/or stabilizing agent. The claims are

simply directed to a known VEGF antagonist in known formulations with known co-solvents, buffers, and/or stabilizing agents.

Although the claims require the formulation to meet "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," the claims (directed to compositions of matter) do not actively require storage of the formulation. The claim is met if a formulation includes a VEGF-specific fusion protein with an organic co-solvent, a buffer, and a stabilizing agent, and the formulation has the property that "at least 98% of the VEGF antagonist is present in "native conformation" following storage at 5° C. for two months as measured by size exclusion chromatography" (the "at least 98%" property).

B. Prosecution History

The application leading to issuance of the '992 patent was filed on October 12, 2018, claiming benefit through a chain of applications to a provisional application filed June 16, 2006. (Ex. 1001 at 1.) The original independent claims included all limitations of the allowed claims, except the "at least 98%" property. (Ex. 1002 (Original claims at 2).)

Patent Owner added the "at least 98%" limitation in response to a double patenting rejection over four patents and a pending application. (Ex. 1002 (2019-04-02 Office Action at 3).) Patent Owner filed a terminal disclaimer over one of

those patents. For the remaining three patents and one pending application, Patent Owner argued that those claims did not "include elements relating to the stability of the VEGF antagonist over time when stored" (i.e., did not include the "at least 98%" property). (Ex. 1002 (2019-07-22 Response to Office Action at 2-6).)

The '992 patent's priority chain includes eight issued patents and the 2006 provisional application. (Ex. 1001 at 1.) 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. (Ex. 1001 at 1; Ex. 1002 (at 2019-07-22 Terminal Disclaimer).)

C. Level of Ordinary Skill

At the time of invention, a person of ordinary skill in the art of the '992 patent would have been a person with a doctorate in biochemistry, pharmacology, or a similar field with at least two years of experience in the development and manufacture of formulations of therapeutic proteins (such as cytokines, growth factors, antibodies, and Fc-fusion proteins) or a similar field. (Ex. 1003 at 51.) A person with less education but more relevant practical experience may also be a person of ordinary skill in the art. (*Id*.)

III. CLAIM CONSTRUCTION

Pursuant to 83 Fed. Reg. 51340, a claim is construed using the standard set forth by *Phillips v. AWH Corp*., 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*).

Petitioner has not proposed any terms for construction because no constructions are necessary to resolve the disputes identified in this Petition. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). Petitioner relies on the plain language of the claims in the '992 patent to demonstrate that the claims are anticipated and/or obvious in light of the prior art. Accordingly, a formal claim construction is unnecessary. *See Hakim v. Cannon Avent Grp., PLC*, 479 F.3d 1313, 1318-19 (Fed. Cir. 2007) ("When there is no dispute as to the meaning of a term that could affect the disputed issues of the litigation, 'construction' may not be necessary."); *Vivid Techs., Inc.*, 200 F.3d at 803 (only those terms that are in controversy need to be construed and only to the extent necessary to resolve the controversy).[2]

IV. THE '992 PATENT IS INVALID

Petitioner respectfully requests the Board cancel all claims of the '992 patent on the following grounds.

Ground 1: Claims 1-18 are anticipated by Fraser (as evidenced by Dix and Holash) under pre-AIA 35 U.S.C. § 102(b) and post-AIA 35 U.S.C. 102(a)(1).

[2] Petitioner reserves the right to propose constructions for claim terms in this proceeding in response to arguments raised by Patent Owner in any future submission.

Ground 2: Claims 1-18 are rendered obvious by Fraser in view of Holash under pre-AIA 35 U.S.C. § 103 and post-AIA 35 U.S.C. § 103.

Ground 3: Claims 1-18 are rendered obvious by Wulff in view of Liu under pre-AIA 35 U.S.C. § 103 and post-AIA 35 U.S.C. § 103.

A. GROUND 1

Fraser is prior art to the '992 patent and discloses a formulation within the scope of the '992 patent's claims. Fraser does not explicitly disclose at least 98% "native conformation" of VEGF antagonist present after storage at 5ºC for two months, but examples in Patent Owner's U.S. Patent No. 8,110,546 ("Dix") (and prosecution thereof) evidence that Fraser's formulation necessarily includes the claimed "at least 98%" property.

As described below, Fraser anticipates each claim.

1. Ground 1 Publications

a. Fraser

Fraser was published in the Journal of Clinical Endocrinology & Metabolism in February 2005.[3] (Ex. 1004 at 1114.) February 2005 is more than one year prior to the '992 patent's earliest possible priority date of June 2006, and,

[3] Fraser also indicates that it was first published online on November 23, 2004. (Ex. 1004 at 1114.)

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 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." (Ex. 1004 at 1114.) Fraser lists Patent Owner, Regeneron, as an employer of at least one of the authors. (Ex. 1004 at 1114.)

Fraser's study was aimed at evaluating the effect of VEGF on pituitary-ovarian function. (Ex. 1004 at 1114.) In the study, macaques were given an injection of a VEGF antagonist. (Ex. 1004 at 1114.) In Fraser's experiments, "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." (Ex. 1004 at 1115.) The Fraser study specifically discloses Regeneron's VEGF Trap: "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.*)

b. Dix

Dix is another Regeneron publication disclosing VEGF formulations and properties thereof. Petitioner does not offer Dix as prior art here but instead offers

Dix "to elucidate what the prior art consisted of." *Hospira, Inc. v. Fresnius 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.* at 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.* at 1329 (internal citations omitted).) Here, Petitioner offers Dix to demonstrate what is necessarily present in Fraser's formulation.

(i) Dix provides evidence of the inherent properties of Fraser

In Dix, Patent Owner disclosed an almost identical formulation to Fraser's: "5 mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 25 mg/ml VEGF trap protein" with pH ranging "from 6.0-6.1." (Ex. 1008 at 11:15-12:20.) During prosecution of Dix, Patent Owner specifically identified Fraser's formulation as one of Dix's two tested formulations: "the completion of two formulations: …(b) 24.3 mg/ml VEGF Trap protein, 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 20% sucrose, and 0.1 % polysorbate-20, pH 6.05, which is the actual lot and formulation used in Fraser." (Ex. 1009 at 2 (citing Ex. 1010) (emphasis added).) As explained in the discussion of limitation

1[E] below, Dix's data shows that the Fraser formulation had at least 98% of VEGF antagonist in "native conformation" following storage at 5° C for two months as measured by size exclusion chromatography.

Regeneron may argue that Dix should not be considered because it is assigned to Regeneron, but the Federal Circuit has repeatedly made it clear that a court (or the Board) can use a patent owner's statements as evidence of inherency. In *Hospira,* the Federal Circuit found that "the work of the inventor or the patentee can be used as the evidence of inherency." (*Hospira* 946 F.3d at 1329 (internal citations omitted).) There, the panel looked to the patentee's new drug application to find the claimed "no more than about 2% decrease in concentration" property was inherent in the prior art. (*Id.* at 1326.) In *Telemac Cellular Corp. v. Topp Telecom, Inc.*, the Federal Circuit found an inherent disclosure based on the patentee's own documents. (247 F.3d 1316, 1327-28 (Fed. Cir. 2007).) In *Astra Aktiebolag v. Andrx Pharms., Inc.*, the only non-expert evidence of inherency before the Federal Circuit panel was the patentee's statements in another litigation. (483 F.3d 1364, 1371-72 (Fed. Cir. 2001).) The panel found that evidence, in conjunction with corroborating expert testimony, sufficient to show the prior art inherently disclosed a missing limitation. (*Id.* at 1373.) Like in *Hospira*, *Telemac*, and *Astra Aktiebolag*, Regeneron's own statements evidence that Fraser inherently discloses the "at least 98%" property. (Ex. 1003 at 93.)

Thus, it is proper to consider Patent Owner's statements in Dix's specification and prosecution history. Those statements show that Fraser inherently discloses at least 98% of the VEGF antagonist is present in "native conformation" following storage at 5° C for two months as measured by size exclusion chromatography. (Ex. 1003 at 93-98.)

2. Fraser anticipates Claim 1

a. Fraser discloses a vial

To the extent Patent Owner argues that the preamble of claim 1 is limiting, Fraser discloses storage of its formulation: "[a]ny compound remaining was stored at 4C and used within 2 wk." (Ex. 1004 at 1115, Left Column.) Storage of formulations commonly occurs in a vial. (Ex 1003 at 102.)

b. Fraser discloses "[1A] a vascular endothelial growth factor (VEGF) antagonist"

Fraser discloses a VEGF antagonist. Specifically, Fraser discloses that "[a]nimals were given a single, iv injection of a potent, receptor-based VEGF antagonist, the VEGF Trap." (Ex. 1004 at Abstract.) Thus, Fraser discloses a VEGF antagonist.

c. Fraser discloses "[1B] an organic co-solvent, a buffer, and a stabilizing agent"

Fraser discloses a co-solvent, a buffer, and a stabilizing agent. For example, Fraser discloses that "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc.,

Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mm phosphate, 5 mm citrate, 100 mm NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Ex. 1004 at Page 1115, Left Column.) Here, Fraser discloses a well-known organic co-solvent (Tween-20), a well-known buffer (phosphate), and a well-known stabilizing agent (sucrose). (Ex 1003 at 92.)

Thus, Fraser discloses an organic co-solvent, a buffer, and a stabilizing agent.

d. Fraser (as evidenced by Holash) discloses "[1C] wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell"

Fraser discloses the VEGF antagonist is a fusion protein: "[c]ompared with earlier versions of receptor-based fusion proteins, the VEGF $Trap_{R1R2}$ exhibits greater affinity for VEGF-A (affinity constant ~1pm) as well as improved bioavailability and pharmacokinetic properties." (Ex. 1004 at Page 1115, Left Column (emphasis added) (citing (Ex. 1007).) In that passage, Fraser cites Holash for the VEGF antagonist, VEGF $Trap_{R1R2}$. (Ex. 1004 at Page 1115, Left Column (citing (Ex. 1007).) Through this citation to Holash for VEGF $Trap_{R1R2}$, one of skill in the art would understand that the Holash VEGF $Trap_{R1R2}$ was the VEGF $Trap_{R1R2}$ in Fraser. (Ex 1003 at 89.) In the next sentence, Fraser continues "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided" and

cites "Reference 21." (Ex. 1004 at 1114.) Because Reference 21 (i.e., Holash) is a Regeneron publication (Ex. 1007 at Title Page), this sentence in Fraser would confirm for one of skill in the art that the VEGF $Trap_{R1R2}$ "provided" to and used in Fraser was the VEGF $Trap_{R1R2}$ described in Holash. (Ex 1003 at 88.)

Holash discloses production of the VEGF antagonist in a CHO cell: "VEGF-$Trap_{R1R2}$ was created by fusing the second Ig domain of $VEGF_{R1}$ with the third Ig domain of $VEGF_{R2}$. All of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells." (Ex. 1007 at 11393-94 (emphasis added).) Thus, the fusion protein provided and used in Fraser was produced in a CHO cell. (Ex. 1003 at 90.)

Thus, Fraser discloses the VEGF antagonist is a fusion protein produced in a CHO cell.

e. Fraser discloses "[1D] 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."

Fraser discloses the fusion protein comprises Ig domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor. For example, Fraser discloses that "[e]ndogenous 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." (Ex. 1004 at Page 1115, Left-Hand Column (emphasis added) (*see also* Ex. 1007 at Figure 1, Page 11394 ("VEGF-Trap$_{R1R2}$ possesses the second Ig domain of VEGFR1 and the third Ig domain of VEGFR2 fused to the Fc portion of human IgG1.").) Fc is a well-known multimerizing component. (Ex. 1003 at 86 (Ex. 1032 at 3).)

Thus, Fraser discloses the fusion protein comprises an Ig domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor and a multimerizing component.

f. Fraser inherently discloses "[1E] 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"

Fraser does not explicitly state that the disclosed formulation has the property that at least 98% of the VEGF antagonist is present in "native conformation" following storage at 5° C for two months as measured by size exclusion chromatography. However, the limitation is inherent in Fraser's formulation as evidenced by the disclosure in Dix, as well as arguments and declarations submitted during prosecution of Dix.

As described above in Section IV.A.1.b, Dix discloses a 25 mg/ml formulation and, based at least on Regeneron's statements in prosecution, a person

of ordinary skill in the art would understand that the Fraser formulation shares the same stability properties as the Dix formulation. (Ex. 1003 at 94.)

Dix Table 9 provides (among other results) the percentage of VEGF antagonist remaining in "native conformation" after storage at 5ºC for two months for Dix's 25 mg/ml formulation. (Ex. 1003 at 95.)

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

(Ex. 1008 at 11:15-12:20.) In fact, Dix reports that the "native conformation" is above 99% after 24 months and still above 98% after 36 months. Thus, Dix evidences for one of skill in the art that the "native conformation" of the Fraser formulation, when stored at 5ºC over two months, is greater than 99% when measured by size exclusion chromatography. (Ex. 1003 at 94-95.)

Even without considering Regeneron's statements during Dix's prosecution, Dix's data independently shows that Fraser's formulation meets the "at least 98%" property. (Ex. 1003 at 96-98.) The differences between the Dix and Fraser formulations are minimal: Fraser discloses 24.3 mg/ml VEGF trap protein and Dix discloses 25 mg/ml. (Ex. 1003 at 96.) One of skill in the art would understand that lower concentration of VEGF trap protein reduces aggregation. (*Id*.) Thus, one of skill in the art would understand that Fraser's 24.3 mg/ml formulation would have at least the same percentage (and actually have slightly better stability) of "native conformation" as Dix's 25 mg/ml formulation after storage. (*Id*.) The other differences would likewise not change the stability: Fraser lists Tween-20 as the organic co-solvent and Dix lists "polysorbate 20", which are synonymous terms[4]; Fraser lists a specific pH 6.0 and Dix lists a range 6.0-6.1 which encompasses Fraser's pH and is within the standard error of pH errors. (Ex. 1003 at 97.)

Thus, the 24.3 mg/ml formulation in Fraser would have at least the same (and, actually, would have better) stability "of the VEGF antagonist present in native conformation following storage at 5° C for two months as measured by size exclusion chromatography" as a 25 mg/ml formulation. (Ex. 1003 at 96.) For at least that reason, Dix's data provides evidence of what is necessarily present in Fraser's formulation.

[4] Tween-20 is a commercial brand name for polysorbate-20. (Ex. 1003 at 116.)

Thus, Fraser explicitly or inherently discloses each limitation of claim 1.

3. Fraser Anticipates Claim 2

Fraser inherently discloses "wherein about 99% or more of the weight of the fusion protein is in native conformation" required by claim 2. As discussed above, Dix reports that the "native conformation" is above 99% after 24 months. (Ex. 1008 at Table 9.) Thus, Fraser's formulation inherently meets "about 99% or more of the weight of the fusion protein is in native conformation."

4. Fraser Anticipates Claim 3

Fraser discloses "wherein the first VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and the human Flt4" required by claim 3. Fraser discloses the first VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and human Flt4. More specifically, Fraser discloses "[e]ndogenous 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." (Ex. 1004 at Page 1115, Left-Hand Column (emphasis added). VEGF-R1 is also known in the art as Flt1; VEGF-R2 is also known in the art as Flk1. (Ex. 1003 at 107-108.)

Thus, Fraser discloses the first VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and the human Flt4.

5. Fraser Anticipates Claim 4

Fraser discloses "wherein the fusion protein comprises amino acids 27-457 of SEQ ID NO:4" required by claim 4. Based on Regeneron's statements in prosecution, one of skill in the art would readily appreciate that the VEGF trap molecule in the Fraser formulation has the amino acid sequence of SEQ ID NO: 4 as described in Dix. (Ex. 1003 at 110.) Fraser's SEQ ID NO: 4 is identical to SEQ ID NO: 4 in the '992 patent. (Ex. 1003 at 111.)

Thus, Fraser discloses the fusion protein comprises amino acids 27-457 of SEQ ID NO:4.

6. Fraser Anticipates Claim 5

Fraser discloses "wherein the VEGF antagonist is a dimer of the fusion protein" required by claim 5. Fc-fusion proteins are well known to form dimers (Ex. 1003 at 114), and Fraser teaches an Fc-fusion protein (Ex. 1003 at 86-88; *citing* Ex. 1004 at 1114-15). Further, Regeneron's VEGF Trap, i.e., the VEGF TrapR1R2 described in Fraser and Holash, is a dimer. (Ex. 1003 at 114.)

Thus, Fraser discloses the VEGF antagonist is a dimer of the fusion protein.

7. Fraser Anticipates Claim 6

Fraser discloses "wherein the organic co-solvent is selected [from] the group consisting of polysorbate 20, polysorbate 90, polyethylene glycol (PEG), PEG3350, and propylene glycol" required by claim 6. Fraser lists Tween-20 as the organic co-solvent. (Ex. 1004 at 1115.) Tween-20 is a commercial brand name for polysorbate-20. (Ex. 1003 at 116.)

8. Fraser Anticipates Claim 7

Fraser discloses "wherein the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol" required by claim 7. Specifically, Fraser teaches that the stabilizing agent is either sucrose or glycerol. (Ex. 1004 at Page 1115, Left Column.)

9. Fraser Anticipates Claim 8

Fraser discloses "wherein the organic co-solvent is polysorbate 20 and the stabilizing agent is sucrose" required by claim 8. Fraser discloses that the co-solvent is Tween-20 and the stabilizing agent is sucrose: "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mm phosphate, 5 mm citrate, 100 mm NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Ex. 1004 at Page 1115, Left Column

(emphasis added).) Tween-20 is a commercial brand name for polysorbate-20. (Ex. 1003 at 116.)

Thus, Fraser discloses the organic co-solvent is polysorbate 20 and the stabilizing agent is sucrose.

10. Fraser Anticipates Claim 9

Fraser discloses "wherein the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose" required by claim 9. (Ex. 1009 at 2 (citing Ex. 1004 at 1115 ("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") (emphasis added); *see also* Ex. 1003 at 122.)

11. Fraser Anticipates Claims 10-18

Claims 1 and 10 differ only in their preamble: claim 1's preamble includes "a vial," and claim 18's preamble includes "a formulation." As described above, Fraser teaches a formulation, and so the preamble's differences have no impact on whether Fraser also anticipates claim 10. Thus, Fraser (as evidenced by Dix) anticipates independent claim 10 for the reasons given above with respect to independent claim 1.

Dependent claims 11-18 are identical to dependent claims 1-9, again except for the preamble "formulation" instead of the preamble "vial," respectively. Thus,

Fraser (as evidenced by Dix) anticipates dependent claims 11-18 for the same reasons given above with respect to dependent claims 2-9. (Ex. 1003 at 104-22)

As demonstrated above, Fraser explicitly or inherently discloses each limitation of each claim of the ’992 patent.

B. GROUND 2

As discussed above in Ground 1, Fraser explicitly or inherently teaches each limitation of all claims of the ’992 patent. Ground 2 demonstrates that Fraser in view of Holash renders obvious all claims of the ’992 patent.

Holash was published in July 2002 (Ex. 1007 at 1), which is more than one year prior to the ’992 patent’s earliest possible priority date of June 2006. 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).

1. Fraser in View of Holash Renders Claim 1 Obvious

a. Fraser in view of Holash renders obvious the claim 1 preamble and limitations [1A]-1[D]

To the extent that Patent Owner argues that the preamble of claim 1 is limiting and not disclosed by Fraser, storage of formulations commonly occurs in a vial. (Ex 1003 at 102.) It would have been obvious to store Fraser’s formulation in a vial because formulations are necessarily stored in a container and vials are routinely used as containers for convenient storage of drug products. (Ex 1003 at 102.)

As discussed above in Section IV.A, Fraser explicitly teaches "[1B] an organic co-solvent, a buffer, and a stabilizing agent." To the extent Patent Owner argues that Fraser does not teach "[1C] wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell," Holash explicitly teaches the VEGF antagonist is a fusion protein produced in a CHO cell: "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." (Ex. 1007 at 11393-94 (emphasis added).)

One of skill in the art, working with Fraser's VEGF Trap $_{R1R2}$ formulation, would have naturally looked to Holash's VEGF Trap $_{R1R2}$ for at least the reason that Fraser specifically references Holash for the benefits of VEGF Trap $_{R1R2}$ and identifies Regeneron (the Holash publisher) as providing the VEGF Trap $_{R1R2}$ used in Fraser. One of skill in the art would have been motivated to use Holash's VEGF Trap $_{R1R2}$ for at least the reason that Holash reports "a very potent high-affinity VEGF blocker that has markedly enhanced pharmacokinetic properties." (Ex. 1003 at 91 (*citing* Ex. 1007 at 11393, Abstract; *id.* at right-column, last full paragraph; 11397, Right Column, First Paragraph.) Holash continues that its "VEGF-Trap effectively suppresses tumor growth and vascularization *in vivo*, resulting in stunted and almost completely avascular tumors" and "may be superior to that achieved by other agents." (Ex. 1003 at 91 (*citing* Ex. 1007 at 11393

Abstract; *id.* at right-column, last full paragraph; 11397, Right Column, First Paragraph.)

As explained above in Section IV.A, Fraser explicitly teaches "[1D] 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." Holash also teaches limitation 1D: "VEGF-Trap$_{R1R2}$ possesses the second Ig domain of VEGFR1 and the third Ig domain of VEGFR2 fused to the Fc portion of human IgG1." (Ex. 1007 at Figure 1, Page 11394.)

b. Fraser in view of Holash renders limitation [1E] obvious

As explained above, Fraser's formulation inherently meets "[1E] 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." Fraser in view of Holash teaches limitation 1[E] because: (1) the Fraser in view of Holash formulation inherently meets the "at least 98%" property; (2) the Fraser in view of Holash formulation is presumed to render obvious the "at least 98%" property because of its similarity to the claimed formulation; and/or (3) one of skill in the art would have been motivated to optimize the Fraser in view of Holash formulation to achieve the "at least 98%" property.

First, Fraser in view of Holash inherently meets limitation 1[E]. As described above in Ground 1, Dix teaches that Fraser's formulation inherently

meets the "at least 98%" property. Storing Fraser's formulation in a vial would have no effect on its stability over two months. (Ex. 1003 at 98.)

Ground 2 offers Holash as explicitly teaching VEGF antagonist production in a CHO cell; this would have no effect on the presence (described above in Ground 1) of the "at least 98%" property for at least the reason that Dix teaches that its formulation includes a VEGF antagonist that was produced in a CHO cell. (Ex. 1008 at Col. 5:12-14.) To the extent Fraser's formulation does not teach production of a VEGF antagonist in a CHO cell, modifying Fraser to produce the VEGF antagonist in a CHO cell would result in the properties disclosed in Dix's formulation. (Ex. 1003 at 91.) Thus, Dix's data is applicable to the Fraser in view of Holash formulation. As described above in Section IV.A.2.f, Dix Table 9 shows that Fraser's formulation produced in a CHO cell has the "at least 98%" property.

Second, the Fraser in view of Holash formulation presumptively renders obvious the "at least 98%" property because "'normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification.'" (*E.I. du Pont v. Synvina*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)).) More specifically, "'when the ranges of a claimed composition overlap the ranges disclosed in the prior art,'" a "prima facie case of obviousness typically exists." (*E.I. du Pont* at 1006 (quoting *In re Peterson,* 315 F.3d 1325,1329 (Fed. Cir. 2003).) Because the Fraser in view

of Holash formulation overlaps (is contained within) the claimed "range," the rebuttable presumption applies here.

Patent Owner cannot rebut that presumption. A patentee may rebut the presumption with evidence of unexpected results. (*E.I. du Pont.* at 1006.) There is nothing unexpected about 98% "native conformation". (Ex. 1003 at 71, 99.) Even if the results were unexpected, Regeneron would still need to show that the claimed ranges are critical (*E.I. du Pont.* at 1006); there are no claimed ranges in the '992 claims, and so Regeneron has no "critical" ranges to point to. A patentee may also rebut the presumption if there is a teaching away in the prior art. (*E.I. du Pont.* at 1006.) Regeneron cannot rebut the presumption because there is no teaching away in Fraser and, to the contrary, Fraser teaches the same excipients as the examples given in the '992 patent. A patentee may rebut the presumption if a parameter was not recognized in the art as results effective. (*E.I. du Pont.* at 1006.) Again, the opposite is true: it was well known in the art that changes in protein and excipient concentrations affects the stability of the resulting formulation. (Ex. 1003 at 69, 100.) One of skill in the art would optimize that stability using known techniques; such optimization is routine in the art. (Ex. 1003 at 100.) Finally, a patentee may rebut the presumption where the prior art discloses broad ranges which do not invite routine optimization. (*E.I. du Pont.* at 1006.) Fraser does not suggest a broad range; the Fraser formulation has the same

excipients, some with almost identical percentages as formulations disclosed in the '992 patent.

Third, one of skill in the art would have optimized the Fraser in view of Holash formulation to achieve the claimed "at least 98%" property. (Ex. 1003 at 101.) "For decades, [the Federal Circuit] and its predecessor have recognized that 'where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.'" (*E.I. du Pont* at 1006 (quoting *In re Aller*, 220 F2d at 456.) Here, the claims include a known composition of VEGF, co-solvent, buffer, and stabilizing agent, and the only additional limitation is the "at least 98%" property. But that property results from changing the concentrations of VEGF, co-solvent, buffer, and stabilizing agent. (Ex. 1003 at 100.) It would have been routine to experiment with Fraser's concentrations to optimize the formulation for percentage of "native conformation" after storage for two months at 5°C. (Ex. 1003 at 100.)

With respect to the claimed temperature, one of skill in the art would have been motivated to maintain a high percentage of VEGF in "native conformation" at 5°C for at least the reason that storage and transportation of such formulations commonly occur at temperatures which include 5°C. (*Id.* at 100.) Thus, it would have been natural for one of skill in the art to optimize Fraser's formulation for 5° C. (*Id.* at 100.) With respect to the claimed percentage, the higher the percentage

of "native conformation", the more efficacious (and hence more commercially viable) and safer the formulation will be at the time the formulation is administered to patients. Finally, the longer the formulation remains efficacious the more commercially viable the formulation will be. Given that transportation and storage can take two months or more, one of skill in the art would have been motivated to optimize "native conformation" for at least two months at 5º C.

The particular percentage (at least 98%) of "native conformation" was not beyond the skill in the art, as evidenced by Patent Owner's disclosure, arguments, and declarations in Dix. As explained above, Dix demonstrates that for the Fraser formulation, after two months at 5ºC, the "native conformation" will still be above 99%. In fact, Dix reports that the "native conformation" was above 99% after 24 months and still above 98% after 36 months. Thus, the claimed 98% "native conformation" was within the skill in the art.

The particular percentage (at least 98%) of "native conformation" was also not an unexpected result. (Ex. 1003 at 71, 99.) As evidenced by Kaisheva '417 (Ex. 1011), Liu (Ex. 1012), and Lam (Ex. 1013), such percentages would have been expected. (Ex. 1003 at 71-76 (citing Ex. 1011, 1012, 1013, 1015 and 1031.))

Thus, one of skill in the art would have been motivated to produce at least 98% of the VEGF antagonist in "native conformation" following storage at 5° C for two months using Fraser, the stability (98% "native conformation") was within

the skill in the art, and the resulting stability (98% "native conformation") would not have been an unexpected result.

Thus, Fraser in view of Holash meets this limitation for at least the reasons, separately and collectively, that the "at least 98%" property is inherent (as evidence by Dix), that one of skill in the art would optimize the formulation for stability to reach the claimed property, and one of skill in the art would have been motivated to produce at least 98% of the VEGF antagonist in "native conformation" following storage at 5° C for two months.

2. Fraser in View of Holash Renders Claim 2 Obvious

Fraser in view of Holash renders obvious "wherein about 99% or more of the weight of the fusion protein is in native conformation." As discussed above, Dix reports that the "native conformation" is above 99% after 24 months. (Ex. 1008 at Table 9.) Thus, the Fraser in view of Holash formulation inherently meets "about 99% or more of the weight of the fusion protein is in native conformation."

Further, given the similarities between Fraser and the disclosed formulations in the '992 patent, Fraser is presumed to meet the 99% "native conformation" remaining and, as explained above, no rebuttals apply.

In addition, one of skill in the art would have routinely varied the concentration of ingredients of a formulation to optimize the percentage of VEGF antagonist remaining in "native conformation" after two months following storage

at 5° C for two months. One of skill in the art would have been motivated to achieve the highest stability possible, which the '992 patent reports is greater than 99%. (Ex. 1003 at 100.) This stability is supported by findings in the prior art. (Ex. 1003 at 71-76.)

Thus, the Fraser in view of Holash renders obvious "about 99% or more of the weight of the fusion protein is in native conformation."

3. Fraser in View of Holash Renders Claim 3 Obvious

Fraser in view of Holash renders obvious "wherein the first VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and the human Flt4." As discussed above in Ground 1, Fraser discloses the first VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and human Flt4. Thus, Fraser in view of Holash renders obvious the first VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and the human Flt4.

4. Fraser in View of Holash Renders Claim 4 Obvious

Fraser in view of Holash renders obvious "wherein the fusion protein comprises amino acids 27-457 of SEQ ID NO:4." Based on Regeneron's statements in prosecution, one of skill in the art would readily appreciate that the VEGF trap molecule in the Fraser formulation has the amino acid sequence of SEQ

ID NO: 4 as described in Dix. (Ex. 1003 at 110.) Fraser's SEQ ID NO: 4 is identical to SEQ ID NO: 4 in the '992 patent. (Ex. 1003 at 111.)

Thus, Fraser in view of Holash renders obvious the fusion protein comprises amino acids 27-457 of SEQ ID NO:4.

5. Fraser in View of Holash Renders Claim 5 Obvious

Fraser in view of Holash renders obvious "wherein the VEGF antagonist is a dimer of the fusion protein." Fc-fusion proteins are well known to form dimers (Ex. 1003 at 114) and Fraser teaches an Fc-fusion protein (Ex. 1003 at 85-87; citing Ex. 1004 at 1114-15). Further, Regeneron's VEGF Trap, i.e., the VEGF $Trap_{R1R2}$ described in Fraser and Holash, is a dimer. (Ex. 1003 at 114.)

Thus, Fraser in view of Holash renders obvious the VEGF antagonist is a dimer of the fusion protein.

6. Fraser in View of Holash Renders Claim 6 Obvious

As discussed above in Ground 1, Fraser discloses the organic co-solvent is selected from the group consisting of polysorbate 20, polysorbate 90, polyethylene glycol (PEG), PEG3350, and propylene glycol. Thus, Fraser in view of Holash renders obvious "wherein the organic co-solvent is selected [from] the group consisting of polysorbate 20, polysorbate 90, polyethylene glycol (PEG), PEG3350, and propylene glycol."

7. Fraser in View of Holash Renders Claim 7 Obvious

As discussed above in Ground 1, Fraser discloses the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol. Specifically, Fraser teaches that the stabilizing agent is either sucrose or glycerol. (Ex. 1004 at Page 1115, Left Column.) Fraser in view of Holash renders obvious "wherein the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol."

8. Fraser in View of Holash Renders Claim 8 Obvious

As discussed above in Ground 1, Fraser teaches the organic co-solvent is polysorbate 20 and the stabilizing agent is sucrose. Thus, Fraser in view of Holash renders obvious "wherein the organic co-solvent is polysorbate 20 and the stabilizing agent is sucrose."

9. Fraser in View of Holash Renders Claim 9 Obvious

Fraser discloses "wherein the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose" required by claim 9. (Ex. 1009 at 2 (citing Ex. 1004 at 1115 ("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") (emphasis added); *see also* Ex. 1003 at 122.)

10. Fraser in View of Holash Renders Claims 10-18 Obvious

Claims 1 and 10 differ only in their preamble: claim 1's preamble includes "a vial," and claim 18's preamble includes "a formulation." As described above, Fraser teaches a formulation, and so the preamble distinctions have no impact on whether Fraser in view of Holash also renders claim 10 obvious. Thus, Fraser in view of Holash renders obvious independent claim 10 for the reasons given above with respect to independent claim 1.

Dependent claims 11-18 are identical to dependent claims 1-9, again except for the preamble "formulation" instead of the preamble "vial." Thus, Fraser in view of Holash renders obvious dependent claims 11-18 for the same reasons given above with respect to dependent claims 2-9. (Ex. 1003 at 104-22.)

As demonstrated above, Fraser in view of Holash renders obvious each limitation of each claim of the '992 patent.

C. GROUND 3

Wulff, another Regeneron VEGF publication, is titled "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2." (Ex. 1005 at 2797.) Wulff, who's authors are also listed on Fraser (Ex. 1003 at 125), is prior art to '992 patent based on its publication date (July 2002), which is more than one year prior to the '992 patent's earliest possible priority date (June 2006).

Wulff describes pre-clinical studies aimed at evaluating the effects of inhibition of thecal angiogenesis on follicular development in the marmoset monkey using VEGF Trap $_{R1R2}$. (Ex. 1005 at 2797, Abstract.) Wulff describes the VEGF antagonists of the '345 patent:

> The 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). The presence of the Fc domain results in homodimerization of the recombinant protein, thereby creating a high affinity (KD1–5pM) VEGF Trap.1 The VEGF trap was expressed in CHO cells and was purified by protein A affinity chromatography followed by size-exclusion chromatography.

(Ex. 1005 at 2798, left column.) The reference also teaches the claimed excipients: an organic co-solvent (Tween-20), a buffer (phosphate), and a stabilizing agent (sucrose). (Ex. 1005 at 2798, Left column.)

Although Wulff does not specifically recite the stability limitation of the '992 patent (i.e., 98% "native conformation" after storage for two weeks at 5º C), it was well-known, long-before the '992 patent's priority date, to optimize stability in pharmaceutical formulations by varying excipient concentrations. As described below, one of skill in the art would have known to vary the percentages of Wulff's protein, organic co-solvents, buffers, and stabilizing agents to optimize stability.

For example, Liu provides guidance for using the claimed combination of excipients in liquid protein formulations to achieve the claimed stability. One of skill in the art would have taken Wulff's pharmaceutical formulations and varied, as demonstrated by Liu, the ingredients' concentrations to arrive at a formulation for optimal stability, including a formulation having at least 98% of the VEGF antagonist in "native conformation" following storage at 5° C for two months as measured by size exclusion chromatography. As described above, one of skill in the art would have been motivated to vary the ingredients' concentrations to optimize the formulation.

Liu, a Genentech PCT application, was filed on March 29, 2004, published on October 7, 2004, and claims priority to a U.S. provisional application filed on April 4, 2003. Liu's publication date (October 7, 2004) is more than one year prior to the '992 patent's earliest possible priority date (June 2006). Thus, Liu qualifies as prior art to the '992 patent.

One of skill in the art would find guidance in Liu for optimizing formulations having a co-solvent (*e.g.*, polysorbate 20), a buffer (*e.g.*, histidine-HCl), and a stabilizer (*e.g.*, trehalose or Arginine HCl) to achieve stable liquid protein formulations having at least 98% "native conformation" after storage at 5° C for two months. For example, the reference provides exemplary concentration ranges for stable formulations: "the present invention concerns a highly

concentrated antibody formulations of low turbidity comprising antibody (40-150 mg/ml), histidine (10-100 mM), sugar (e.g., trehalose or sucrose, 20-350 mM) and polysorbate (0.01%-0.1%)." (Ex. 1012 at ¶ [0013].)

In Table 1, Liu reports two liquid protein formulations having >98% monomer after storage at 5ºC for 3 months (*i.e.*, 99.3% and 98.8% respectively) or longer. Both protein formulations contain polysorbate 20, and one protein formulation further contains trehalose.

TABLE 1

Analytical Methods

Assay	Purpose
Color, Clarity, Appearance[a]	Visual inspection of liquid formulations
Size Exclusion Chromatography (SEC)[b]	Measures % monomer, soluble aggregates and low molecular weight components
Hydrophobic Interaction Chromatography (HIC)[c]	Measures level of Asp-32 isomerization and free thiol
UV Spec Scan (Gravimetric)[f]	Measures protein concentration
Turbidity (Mean OD 340–360 nm)[d]	Measures soluble and insoluble aggregates
Activity[e]	Determines binding activity of anti-IgE

Summary of Liquid Formulations

Formulations	Protein Ranges	Buffer/Ranges	Excipients/Ranges
80 mg/ml E25 50 mM Histidine-HCl 150 mM Trehalose 0.05% Polysorbate 20 pH 6.0	40–150 mg/ml	His-HCl or His-Acetate Ranges: 10 mM–100 mM	Trehalose or Sucrose Sugar Ranges: 20 mM–350 mM Polysorbate: 0.01%–0.1%
150 mg/ml E25 20 mM Histidine-HCl 200 mM ArgHCl 0.02% Polsorbate 20 pH 6.0	40–260 mg/ml	His-HCl or His-Acetate Ranges: 10 mM–100 mM	ArgHCl Ranges: 50 mM–200 mM Polysorbate: 0.01%–0.1%

Temp (° C.)	Time (months)	Visual	pH	SEC[a] % Monomer	HIC[b] % of Main	Potency[c]	Turbidity[d]
		Stability Data for 150 mg/ml E25 in Histidine and ArgHCl formulation					
5	0	pass	6.2	99.0	64	106	0.25
	1	pass	6.0	99.2	63	100	0.27
	3	pass	6.0	99.3	63	111	0.25
	16	pass	6.0	98.9	62	83	0.27
30	1	pass	5.9	98.43	54	91	0.25
	3	Pass	6.1	97.53	42	65	0.30
	16	Pass	6.0	90.63	19	28	0.54
		Stability Data for 80 mg/ml E25 in Histidine and Trehalose formulation					
5	0	Pass	5.7	99.1	64	100	0.20
	1	Pass	5.8	98.7	63	92	0.20
	3	Pass	5.7	98.8	63	124	0.20
	6	Pass	5.7	99.1	63	97	0.21
	14	Pass	5.7	99.0	62	83	0.21
	24	Pass	5.7	98.8	62	84	0.20
30	1	Pass	5.8	98.7	55	77	0.20
	3	Pass	5.7	97.4	41	76	0.29

(Ex. 1012 at 26-27.)

1. Wulff in View of Liu Render Claim 1 Obvious

a. Wulff renders obvious storage in "a vial"

To the extent Patent Owner argues that the preamble of claim 1 is limiting, use of a vial to contain a formulation is well within the knowledge of a person of ordinary skill. (Ex. 1003 at 145.) Storage of Wulff's formulation in a vial is obvious. (*Id.*)

b. Wulff teaches "[1A] a vascular endothelial growth factor (VEGF) antagonist"

Wulff discloses a VEGF antagonist. (Ex. 1003 at 126.) For example, Wulff teaches fusing a receptor to VEGF Trap $_{R1R2}$ in order to "inhibit vascular endothelial growth factor (VEGF)." (Ex. 1005 at 2797; *see also id.* at 2804 (describing the VEGF Trap $_{R1R2}$ molecule as an "a novel antagonist" that inhibits VEGF).)

c. Wulff teaches "[1B] an organic co-solvent, a buffer, and a stabilizing agent"

Wulff discloses a co-solvent, a buffer, and a stabilizing agent in its formulation. Wulff teaches that marmosets were dosed with VEGF trap. (Ex. 1005 at 2798, Left column.) To one of skill in the art, this teaches that the Wulff animals were administered a liquid formulation of the VEGF antagonist. (Ex. 1003 at 131.)

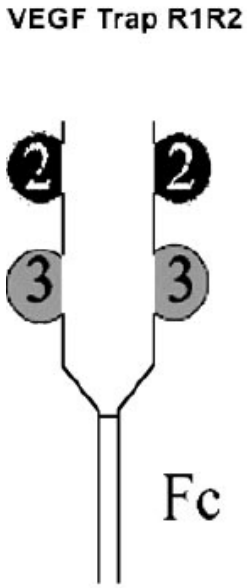
Furthermore, Wulff teaches that control animals "were treated with vehicle containing 5 mM phosphate, 5 mM citrate, 100 mM sodium chloride, 0.1% (wt/ vol) Tween 20, and 20% (wt/ vol) sucrose." (Ex. 1005 at 2798, Left column.) One of skill in the art would understand that the control vehicle's formulation is the same as the medicinally active agent (VEGF Trap in Wulff). (Ex. 1003 at 131 (quoting Ex. 1033 at 1 ("a carrier or inert medium used as a solvent (or diluent) in which a medicinally active agent is formulated and or administered."); Ex. 1034 at 1 (explaining that in a pre-clinical animal study, animals in a vehicle control group "receive treatment with the vehicle in which the experimental substance is dissolved or suspended").)

Thus, Wulff teaches an organic co-solvent, a buffer, and a stabilizing agent.

d. Wulff teaches "[1C] wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell" and "[1D] 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."

Wulff teaches that VEGF Trap $_{R1R2}$ 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 Ig (Fig. 1)." (Ex. 1005 at 2798, left column.)

As explained in Wulff and illustrated in Fig. 1C (reproduced below), the "presence of the Fc domain results in homodimerization of the recombinant protein." (Ex. 1005 at 2798, left column.)



The Fc domain serves as a multimerizing component in the VEGF Trap $_{R1R2}$ molecule. (Ex. 1003 at 128.)

CHO cell production is also taught by Wulff: "VEGF trap was expressed in CHO cells." (Ex. 1005 at 2798, left column.)

Thus Wulff teaches "the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell" and "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." (Ex. 1003 at 127-30.)

e. Wulff in view of Liu renders obvious "[1E] 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"

Wulff does not explicitly describe the stability of the formulation. However, the claimed stability property is obvious. A person of ordinary skill in the art would have been motivated to determine and optimize the stability of the formulation because stability data is required in the FDA approval process to determine the shelf life of a protein therapeutic. (Ex. 1003 at 134.)

It was common in the art to measure the formulation stability upon storage for a period of time including two months under refrigerated conditions such as 5°C. (Ex. 1003 at 135.) As protein aggregation is associated with decreased protein activity and increased immunogenicity, a person of ordinary skill in the art would have been motivated to minimize the amount of aggregates following storage. (*Id.*) Further, the claimed measure of stability by size exclusion chromatography is a commonly used assay to analyze the physical stability of protein formulations by assessing the amount of protein aggregates. (*Id.*)

One of skill in the art would have been motivated to start with Wulff's formulation and optimize it. (Ex. 1003 at 134.) Wulff's formulation has the same VEGF antagonist (VEGF Trap $_{R1R2}$), excipients, and excipient concentrations as Fraser. (Ex. 1003 at 133.) Thus, Regeneron did not change the excipients or their

concentrations in the formulation of the VEGF antagonist from 2002 to 2005. (*Id.*) This would lead one of skill to understand that Wulff's formulation is favorable for the VEGF antagonist molecule, thereby providing a good starting point for a person of ordinary skill in the art to optimize a VEGF-Trap formulation. (*Id.*)

One of skill in the art would have looked to a teaching like Liu to optimize Wulff's formulation. (Ex. 1003 at 138.) Although Liu teaches antibodies as active agents (instead of Fc-fusion proteins), antibodies and Fc-fusion proteins have similar molecular weights and structures. (Ex. 1003 at 141.) Further, the Fc region accounts for more than 40% the molecular weight of a full-length antibody and a typical Fc-fusion protein. (*Id.*) Those skilled in the art routinely consulted antibody formulation literature for guidance on formulation of Fc-fusion proteins. (*Id.*)

Furthermore, a person of ordinary skill would have reasonable expectation that an optimized liquid formulation would have at least 98% "native conformation" after storage of the liquid formulations at 5ºC for 2 months as measured by size exclusion chromatography. (Ex. 1003 at 142.) Such stability was well known in the art. (Ex. 1003 at 71-76.)

Although Wulff does not explicitly disclose the concentration of VEGF Trap in its formulation, 25 mg/mL is a commonly used concentration for VEGF antagonist; for example, the FDA-approved drug AVASTIN® (a VEGF antagonist)

is formulated at 25 mg/mL. (Ex. 1003 at 144.) With a 25 mg/mL concentration of VEGF antagonist and a pH of 6.0, Wulff's formulation is identical to Dix. (Ex. 1003 at 144.) As discussed earlier, Dix provides evidence that a person of ordinary skill optimizing a Wulff formulation with 25 mg/mL VEGF Trap could readily achieve at least 98% "native conformation" following storage at 5° C for two months as measured by size exclusion chromatography.

2. Wulff in View of Liu Renders Claim 2 Obvious

Liu Table 1 discloses a liquid protein formulation having >99% "native conformation" after storage at 5ºC for 3 months or longer. (Ex. 1012 at Table 1.) Thus, one of ordinary skill in the art could optimize Wulff's formulation and have a reasonable expectation of achieving the claimed formulation, as shown by Liu. (Ex. 1003 at 147; *see also* Ex. 1008 at Table 9 (reporting that "native conformation" above 99% after 24 months).) Wulff in view of Liu thus renders claim 2 obvious.

3. Wulff in View of Liu Renders Claim 3 Obvious

Wulff discloses "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 Ig (Fig. 1)." (Ex. 1005 at 2798, left column.) VEGF-R2 is

also known in the art as Flk1. (Ex. 1003 at 148.) Wulff in view of Liu thus renders claim 3 obvious.

4. Wulff in View of Liu Renders Claim 4 Obvious

Because Wulff discloses the same VEGF Trap $_{R1R2}$ molecule as Fraser and Dix, the sequence alignment in Ground 1 is also applicable to Wulff. (Ex. 1003 at 149.) That sequence alignment shows that Dix (and Wulff) is 100% identical to the amino acid sequence of SEQ ID NO: 4 in the '992 patent. (*Id.*) Thus, Wulff in view of Liu renders obvious the fusion protein comprises amino acids 27-457 of SEQ ID NO:4.

5. Wulff in View of Liu Renders Claim 5 Obvious

Wulff in view of Liu renders obvious "wherein the VEGF antagonist is a dimer of the fusion protein." Wulff states that the "presence of the Fc domain results in homodimerization of the recombinant protein." (Ex. 1005 at 2798, left column.) Thus, Wulff discloses a VEGF antagonist that is a dimer of the fusion protein and Wulff in view of Liu renders claim 5 obvious. (Ex. 1003 at 150.)

6. Wulff in View of Liu Renders Claim 6 Obvious

Wulff discloses a formulation containing 0.1% (wt/ vol) Tween20, which is polysorbate 20. (Ex. 1005 at 2798, left column.) A person of ordinary skill would have been led by Wulff to choose an organic co-solvent from the group consisting of polysorbate 20, polysorbate 90, polyethylene glycol (PEG), PEG3350, and

propylene glycol. (Ex. 1003 at 151.) Thus, Wulff in view of Liu renders claim 6 obvious.

7. Wulff in View of Liu Renders Claim 7 Obvious

Wulff discloses a formulation containing 20% (wt/ vol) sucrose. (Ex. 1005 at 2798, left column.) Wulff in view of Liu thus renders obvious "wherein the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol." (Ex. 1003 at 152.)

8. Wulff in View of Liu Renders Claim 8 Obvious

Wulff discloses a formulation containing 0.1% (wt/ vol) polysorbate 20 and 20% (wt/ vol) sucrose. (Ex. 1005 at 2798, left column.) A person of ordinary skill would have been led by Wulff to choose polysorbate 20 as the organic co-solvent, and sucrose as the stabilizing agent and would have had a reasonable expectation of success of achieving the claimed stability, as explained above with respect to claim 1. (Ex. 1003 at 153.)

Thus, Wulff in view of Liu renders obvious "wherein the organic co-solvent is polysorbate 20 and the stabilizing agent is sucrose."

9. Wulff in View of Liu Renders Claim 9 Obvious

Wulff in view of Liu renders obvious "wherein the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose." Wulff discloses a formulation containing 5 mM phosphate, 0.1% (wt/ vol)

polysorbate 20, and 20% (wt/ vol) sucrose. (Ex. 1005 at 2798, left column.) A person of ordinary skill would have been led by Wulff to choose polysorbate 20 as the organic co-solvent, phosphate as the buffer, and sucrose as the stabilizing agent and would have had a reasonable expectation of success. (Ex. 1003 at 154.)

10. Wulff in View of Liu Renders Claims 10-18 Obvious

Claims 1 and 10 differ only in their preamble: claim 1's preamble includes "a vial," and claim 18's preamble includes "a formulation." As described above, Wulff teaches a formulation, and so the preamble distinctions have no impact on whether Wulff in view of Liu also renders claim 10 obvious. Thus, Wulff in view of Liu renders obvious independent claim 10 for the reasons given above with respect to independent claim 1.

Dependent claims 11-18 are identical to dependent claims 1-9, again except for the preamble "formulation" instead of the preamble "vial." Thus, Wulff in view of Liu renders obvious dependent claims 11-18 for the same reasons given above with respect to dependent claims 2-9. (Ex. 1003 at 147-54.)

As demonstrated above, Wulff in view of Liu renders obvious each limitation of each claim of the '992 patent.

V. SECTION 325(d) IS INAPPLICABLE

Section 325(d) is inapplicable to this proceeding because the Petition does not raise substantially the same art or arguments in the same way as the

examination of the ’992 patent. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, at 7-11 (P.T.A.B. Feb. 13, 2020) (precedential).

None of the references analyzed in this petition were cited on the record during prosecution. Although some of the references were cited in an information disclosure statement, “[t]he Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution.” *Amgen Inc. v. Alexion Pharma., Inc.*, IPR2019-00740, Paper 15 at 65-66 (P.T.A.B. Aug. 30, 2019).

Further, no reference cited herein is cumulative of any reference analyzed during prosecution. During prosecution, the Office issued a single rejection for obviousness-type double patenting over patents and applications in the ’992 family. No rejection was made based on the stability of the formulation inherently disclosed in any reference, much less Fraser. Nor was any rejection premised on the obviousness of the stability property in view of known formulations.

VI. STANDING

Petitioner certifies that the ’992 patent is available for inter partes review, that Petitioner has not been served with a complaint alleging infringement of the ’992 patent more than one year prior to the filing of this Petition, that Petitioner

has not filed a civil action challenging the validity of the '992 patent, and that Petitioner is not barred or estopped from requesting *inter partes* review challenging the claims of the '992 patent on the grounds identified in this Petition.

VII. NOTICES AND STATEMENTS

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Pursuant to 37 C.F.R. § 42.8(b)(1), the real parties-in-interest in this proceeding are Chengdu Kanghong Biotechnology Co., Ltd. (Petitioner), Chengdu Kanghong Pharmaceutical Group Co., Ltd. (the parent company of Petitioner), and Beijing Kanghong Biomedical Co., Ltd. (a wholly owned subsidiary of Petitioner's parent company). No other party has funded or exercises control over this Petition.

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

Petitioner is unaware of any related federal court or PTAB proceedings. Petitioner is aware of a co-pending *ex parte* reexamination proceeding (Control No. 90/014,448) involving the '992 patent.

C. Lead and Back-up Counsel Under 37 C.F.R. § 42.8(b)(3)

Lead Counsel for Petitioner	Backup Counsel for Petitioner
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Pursuant to 37 C.F.R. § 42.8(b)(4), service information for lead and back-up counsel is provided above. Petitioner consents to electronic service by email to CHENGDU-IPR@mofo.com.

VIII. CONCLUSION

For the foregoing reasons, there is a reasonable likelihood that Petitioner will prevail as to the all claims of the '992 patent. Accordingly, Petitioner request *inter partes* review of all claims.

The PTO is authorized to charge any required fees, including the fee as set forth in 37 C.F.R. § 42.15(a) and any excess claim fees, to Deposit Account No. **03-1952** referencing Docket No. **77688-00000.11**.

Dated: January 7, 2021

By */ Matthew I. Kreeger /*

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

I hereby certify that this Petition for *Inter Partes* Review has 10,034 words (as counted by the "Word Count" feature of the Microsoft Word™ word-processing system), exclusive of "a table of contents, a table of authorities, mandatory notices under § 42.8, a certificate of service or word count, or appendix of exhibits or claim listing."

Dated: January 7, 2021

By */ Matthew I. Kreeger /*
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Registration No. 56,398

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

I hereby certify that the attached Petition for *Inter Partes* Review and supporting materials were served as of the below date by UPS, which is a means as fast and reliable as U.S. Express Mail, on the Patent Owner at the correspondence address indicated for U.S. Patent No. 10,464,992:

A&P – Regeneron
601 Massachusetts Ave., NW
Washington DC 20001

Dated: January 7, 2021

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