

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re <i>Ex Parte</i> Reexamination of:	Furfine et al.
Filing Date:	Not Yet recorded
U.S. Patent No.:	10,464,992
Date of Issuance:	November 5, 2019
Appl. Ser. No.	16/159,269
Date of Appl. Filing:	October 12, 2018
Title:	VEGF Antagonist Formulations Suitable for Intravitreal Administration

VIA EFS
Mail Stop "Ex Parte Reexam"
Attn: Central Reexamination Unit
Commissioner for Patents
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Alexandria, VA 22313-1450

**REQUEST FOR *EX PARTE* REEXAMINATION OF
U.S. PATENT NO. 10,464,992 (Furfine et al.)**

Dear Sir:

Requester requests reexamination, pursuant to 35 U.S.C. §§ 301-307 and 37 C.F.R. § 1.510 et seq. of all claims (claims 1-18) of U.S. Patent No. 10,464,992 to Furfine *et al* ("the '992 Patent," Exhibit 1), which issued on November 5, 2019 from U.S. Patent Application No. 16/159,269 filed on October 12, 2018.

U.S. Patent and Trademark Office assignment records indicate that the '992 Patent is currently assigned to Regeneron Pharmaceuticals, Inc. ("Patent Owner"), located at 777 Old Saw Mill River Road, Tarrytown, New York 10591-6707. The term of the '992 Patent has not yet expired.

Requester certifies that it is not subject to the estoppel provisions of 35 U.S.C. §§ 315(e)(1) and 325(e)(1).

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EXHIBIT LIST

<i>Exhibit No.</i>	<i>Document Description</i>
1	U.S. Patent No. 10,464,992 B2, issued on Nov. 5, 2019, to Furfine et al.
2	U.S. Patent No. 7,608,261 B2, issued on Oct. 27, 2009, to Furfine et al.
3	U.S. Patent No. 9,340,594 B2, issued on May 17, 2016, to Furfine et al.
4	U.S. Patent No. 9,914,763 B2, issued on Mar. 13, 2018, to Furfine et al.
5	U.S. Patent No. 10,400,025 B2, issued on Sept. 3, 2019, to Furfine et al.
6	U.S. Patent No. 9,580,489 B2, issued on Feb. 28, 2017, to Furfine et al.
7	Papadopoulos et al., International Patent Application Publication No. WO 00/75319 A1, published on Dec. 14, 2000
8	Vitti et al., U.S. Patent Application Publication No. 2016/0144025 A1, published on May 26, 2016
9	Baca et al., International Patent Application Publication No. WO 98/45331 A2, published on Oct. 15, 1998
10	Cunningham et al., International Patent Application Publication No. WO 00/63380 A1, published on Oct. 26, 2000
11	Prosecution history for U.S. Patent Application No. 16/159,269 (U.S. Patent No. 10,464,992)

I. INTRODUCTION

Requester hereby requests *ex parte* reexamination of claims 1-18 of U.S. Patent No. 10,464,992 (“the ’992 Patent”, Exhibit 1) to inventors Furfine et al., owned by Regeneron Pharmaceuticals, Inc. (“Patent Owner”), pursuant to 35 U.S.C. §§ 301-307 and 37 C.F.R. § 1.510 et seq. The basis of this request is that claims 1-18 of the ’992 Patent are invalid for non-statutory obviousness-type double patenting over the claims of three earlier-expiring patents assigned to Patent Owner:

1. U.S. Pat. No. 7,608,261 (“the ’261 Patent,” Exhibit 2);
2. U.S. Pat. No. 9,340,594 (“the ’594 Patent,” Exhibit 3); and
3. U.S. Pat. No. 9,580,489 (“the ’489 Patent,” Exhibit 6).

This request is within the proper time period for filing because it is during the period of enforceability of the ’992 Patent as defined in MPEP § 2209. The ’992 Patent expires on June 14, 2027 because it lists June 14, 2007 as the earliest effective filing date on its face and has no Patent Term Adjustment. *See* 35 U.S.C. §§ 154(a)(2), (b) (pre-AIA). Patent Owner is the current assignee of each of the ’261, ’594, and ’489 Patents (collectively referred to herein as the “OTDP Reference Patents”).

The claims of the ’992 Patent are directed to a formulation (or vial containing a formulation) for a small genus of vascular endothelial growth factor (“VEGF”) antagonist fusion proteins, including the fusion protein now known as aflibercept. Aflibercept is marketed by Patent Owner as Eylea®. Each OTDP Reference Patent claims a *more specific* formulation that falls within the scope of the ’992 Patent claims, or claims an obvious variant of the ’992 Patent claims. The ’992 Patent is in the same family as the OTDP Reference Patents (“the Furfine Family”), but has a term that is over *six years* longer than claims of those three commonly owned OTDP Reference Patents.

This is precisely the type of unjustified timewise extension of the right to exclude granted by a patent that obviousness-type double patenting was designed to protect against. Requester therefore requests *ex parte* reexamination of the '992 Patent based on the substantial new questions of patentability described herein, and requests that all claims (claims 1-18) be rejected on grounds of non-statutory obviousness-type double patenting.

II. BACKGROUND

A. Subject Matter Claimed in the '992 Patent

The '992 Patent contains two broad and substantively identical independent claims that recite:

A vial [or formulation]¹ comprising:

a vascular endothelial growth factor (VEGF) antagonist,

an organic co-solvent,

a buffer, and

a stabilizing agent,

wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a 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.

'992 Patent at 19:31-43 and 19:65-20:40.

Claim 3 of the '992 Patent is dependent on claim 1 and narrows the genus of VEGF

¹ Independent claim 10 is identical to claim 1 except it recites the word “formulation” instead of the word “vial” in its preamble.

antagonist to a fusion protein “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.” *Id.* at 19:46-48. Claim 4 of the ’992 Patent is dependent on claim 3 and further narrows the genus of VEGF antagonist to a fusion protein comprising “amino acids 27-457 of SEQ ID NO:4.” *Id.* at 19:49-50. Thus, the claims of the ’992 Patent demonstrate that the VEGF antagonist comprising amino acids 27-457 of SEQ ID NO:4 (aflibercept) as recited in claim 4 is a species within the scope of each of claims 1 and 3.

The ’992 Patent does not define the phrase “organic co-solvent,” but provides open-ended examples thereof, *e.g.*, “the organic co-solvent may be polysorbate, for example, polysorbate 20 or polysorbate 80, polyethylene glycol (PEG), for example, PEG 3350, or propylene glycol, or a combination thereof.” *Id.* at 2:25-28.

The ’992 Patent does not define the term “buffer,” but provides open-ended examples thereof, *e.g.*, “the buffering agent may be, for example, phosphate buffer. In a specific embodiment, the phosphate buffer is a sodium phosphate buffer.” *Id.* at 2:31-34.

The ’992 Patent does not define the term “stabilizing agent,” but provides open-ended examples thereof, *e.g.*, “the stabilizing agent may be sucrose, sorbitol, glycerol, trehalose, or mannitol.” *Id.* at 2:30-31.

Both of the independent claims of the ’992 Patent recite an intended result of the formulation, *i.e.*, “at least 98% of the VEGF antagonist is present in native conformation following storage at 5°C. for two months as measured by size exclusion chromatography.” *Id.* at claims 1 and 10. While the phrase “native conformation” is not used in the ’992 specification, the similar phrase “Native Configuration” is used in the Tables in Examples 1-8 when reporting the size exclusion chromatography (“SEC”) results. Those examples of the ’992 Patent (and

each of the OTDP Reference Patents) provide experimental data which evidence that all formulations tested had at least 98% of the VEGF antagonist present in native configuration following storage at 5°C for two months as measured by SEC. *Id.* at 8:8–12:18, Tables 1-8. For example, for the formulation tested in Example 3 of the '992 Patent (which is covered by the claims of, and identically reported in, each of the OTDP Reference Patents), 99.2% of the VEGF antagonist was present in native configuration after two months of storage at 5°C:

Example 3. Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5° C. in 3 ml Glass Vials					
[0060] A liquid formulation containing 40 mg/ml VEGF Trap (SEQ ID NO: 4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5° C. in 3 ml glass vials and samples tested at 0.5, 1, 2, 3, and 4 months. Stability results are shown in Table 3. Turbidity, percent recovered protein and purity was determined as described above.					
TABLE 3					
Stability of 40 mg/ml VEGF Trap Protein (VGFT-SS207)					
Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.3	100	99.5
0.5	Pass	0.00	6.3	99	99.4
1	Pass	0.00	6.2	98	99.5
2	Pass	0.00	6.2	95	99.2
3	Pass	0.01	6.4		
4	Pass	0.01	6.3		

The '992 Patent claims 2-9 are ultimately dependent from claim 1. Claim 2 specifies that “about 99% or more of the weight of the fusion protein is in native conformation.” *Id.* at 19:44-45. Claims 3 and 4 further specify the VEGF antagonist fusion protein, as explained above. *Id.* at 19:46-50. Claim 5 specifies that “the VEGF antagonist is a dimer of the fusion protein.” *Id.* at 19:51-52. Claim 6 specifies that “the organic co-solvent is selected for [sic] the group consisting

of polysorbate 20, polysorbate 90, polyethylene glycol (PEG), PEG3350, and propylene glycol.” *Id.* at 19:53-56. Claim 7 specifies that “the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.” *Id.* at 19:57-59. Claim 8 specifies that “the organic co-solvent is polysorbate 20 and the stabilizing agent is sucrose.” *Id.* at 19:60-61. Claim 9 specifies that “the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose.” *Id.* at 19:62-64. Claims 11-18 are ultimately dependent on claim 10, but are otherwise identical to dependent claims 2-9, respectively. *See id.* at 20:41-64.²

B. State of the Art at the Time of the Application for the '992 Patent

The '992 Patent claims priority through a series of applications to U.S. Provisional Application No. 60/814,484, filed on June 16, 2006. Prior to June 16, 2006, VEGF-specific fusion protein antagonists were well known. For example, Patent Owner’s PCT Publication WO 00/75319 A1 (“Papadopoulos,” Exhibit 7), published December 14, 2000, disclosed the exact same VEGF antagonist fusion proteins disclosed and claimed in the '992 Patent.

Papadopoulos teaches amino acid sequences encoding VEGF antagonist fusion proteins that fall within the scope of the independent claims of the '992 Patent, including a protein called “Flt1D2.Flk1D3.FcΔC1(a),” which corresponds to SEQ ID NO: 2 of the '992 Patent, and a protein called “VEGFR1R2-FcΔC1(a),” which corresponds to SEQ ID NO: 4 of the '992 Patent and is now known as “aflibercept.” Ex. 7, 26:12-25; Ex. 8 ¶ [0086]. The nucleotide and amino acid sequences of VEGFR1R2-FcΔC1(a) are provided in Papadopoulos Figs. 24A-24C. Ex. 7, 22:1-2. As shown in Appendix E, the amino acid sequence of the VEGFR1R2-FcΔC1(a) protein

² Claim 11 of the '992 patent issued with a typographical error in which the recitation of “90%” after “99%” was not deleted. Patent Owner filed a Request for a Certificate of Correction on February 7, 2020, requesting deletion of the recitation of “90%” from claim 11. Requester has used the corrected version of claim 11 in this Request for Reexamination.

in Papadopoulos is 100% identical to SEQ ID NO: 4 of the '992 Patent (and each of the OTDP Reference Patents).

Patent Owner's post-filing U.S. Pub. No. 2016/0144025 (the "Vitti Publication," Exhibit 8) confirms that "VEGFR1R2-Fc Δ C1(a)" is "also known as aflibercept." Ex. 8 ¶ [0086]. Vitti teaches that aflibercept is "encoded by the amino acid sequence of SEQ ID NO: 11." *Id.* As shown in Appendix D, SEQ ID NO: 11 of the Vitti Publication is 100% identical to SEQ ID NO:4 of the '992 Patent (and each of the OTDP Reference Patents). Vitti also explains that aflibercept "consists of a dimer of two polypeptides consisting of amino acids 27-457 of [SEQ ID NO:4 of the '992 patent]." Ex. 8 ¶ [0197]. As was known in the prior art, the complete SEQ ID NO:4 includes, *inter alia*, a signal peptide that is removed during protein production, and an Fc sequence of human IgG that causes the protein to dimerize. *See* Ex. 7, Fig. 24A (identifying the signal sequence at amino acids 1-26 of SEQ ID NO: 4), Figs. 24B-C (identifying the human Fc region "hFC Δ C1A" at amino acids 232-458). Accordingly, the VEGF fusion protein of SEQ ID NO:4 and the dimerized VEGF fusion protein consisting amino acids 27-457 of SEQ ID NO:4 both refer to aflibercept, as known in the prior art.

Papadopoulos also teaches that these VEGF antagonist fusion proteins were produced in recombinant Chinese hamster ovary (CHO) cells. *See id.* at 67:25-68:5 ("The process for production of Flt1D2.Flk1D3.Fc Δ C1(a) [*i.e.*, the protein of SEQ ID NO: 2 of the '992 Patent] protein... involves suspension culture of recombinant Chinese hamster ovary (CHO K1/E1A) cells which constitutively express the protein product. The cells are grown in bioreactors and the protein product is isolated and purified by affinity and size exclusion chromatography."). Papadopoulos also discloses that "CHO transiently expressed VEGFR1R2-Fc Δ C1(a) [*i.e.*, the protein of SEQ ID NO: 4 of the '992 Patent]." *Id.* at 82:12-13.

It was also well known in the art at the time of the alleged invention to place VEGF antagonist formulations in vials. *See, e.g.*, WO 1998/045331 A2, 47:13-18 (Exhibit 9); WO 2000/063380 A1, 23:6-10, 25:20-26 (Exhibit 10), (collectively referred to herein as “Exemplary Vial Pubs.”).

C. Prosecution History of the '992 Patent

The '992 Patent was filed as U.S. Patent Application No. 16/159,269 on October 12, 2018 and issued on November 5, 2019.³ In an Office Action dated April 2, 2019, all claims of the '992 Patent were rejected on grounds of non-statutory obviousness-type double patenting over five commonly owned patent references: U.S. Pat. No. 8,092,803; the '261 Patent; the '594 Patent; U.S. Pat. No. 9,914,763 (“the '763 Patent,” Exhibit 4); and Application Serial No. 15/879,294 (“the '294 Application”), now issued as U.S. Pat. No. 10,400,025 (“the '025 Patent,” Exhibit 5). Office Action dated April 2, 2019, at ¶¶ 9-13. In response to those rejections, Patent Owner:

- 1) Filed a terminal disclaimer over U.S. Pat. No. 8,092,803;
- 2) amended the independent claims to add the phrase “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”; and
- 3) argued that the new “element relating to stability” or “elements relating to the percentage of the VEGF antagonist which maintains its conformation following storage over a period of time” are “not contained” within any of the claims of the prior patents.

See Response to Non-Final Office Action and Amendment dated July 22, 2019, at 5-6.

³ The prosecution history of the '992 Patent is attached as Exhibit 11.

Patent Owner also argued that the process of production in CHO cells is “not contained” in the claims of the ’594 Patent and the ’294 Application. *See id.* at 5-6.

The Examiner issued a Notice of Allowance stating only that the rejections were “withdrawn in view of the amended claims and the terminal disclaimer.” Notice of Allowance dated August 21, 2019, at 2.

A substantial new question of patentability exists based on obviousness-type double patenting over at least the earlier-expiring ’261 and ’594 Patents, because the Examiner incorrectly concluded that the stability result language rendered the claims of the ’992 Patent patentably distinct from the claims of Patent Owner’s earlier-expiring patents. It does not, as explained in detail below. *See, e.g.,* Section V.E.1.b. *infra*.

The Examiner did not cite the ’489 Patent at all during the brief prosecution, and a substantial new question of patentability exists based on obviousness-type double patenting over that patent for the reasons discussed below.

III. CLAIM CONSTRUCTION

In reexamination, claims are given their broadest reasonable interpretation (“BRI”) consistent with the specification. *In re Yamamoto*, 740 F.2d 1569, 1571 (Fed. Cir. 1984); *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1259 (Fed. Cir. 2010); MPEP § 2258(I)(G). Only terms in controversy need be construed, and only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). Application of the ordinary and customary meanings of broad terms such as “vascular endothelial growth factor (VEGF) antagonist,” “organic co-solvent,” “buffer,” and “stabilizing agent” is sufficient for claim construction purposes. Moreover, the claim language of the ’992 Patent is also used in the claims and specifications of each of the OTDP Reference Patents. Thus, because the same terms used in the ’992 Patent claims are also used in the claims of the

OTDP Reference Patents, which share the same specification as the '992 Patent, the meanings of the claim terms are not in controversy and it is not necessary to construe them.

With regard to the recited phrase “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,” the Federal Circuit has repeatedly held that claim terms that “only state an intended result” are non-limiting. *See, e.g., In re Copaxone Consol. Cases*, 906 F.3d 1013, 1023 (Fed. Cir. 2018); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374-75 (Fed. Cir. 2001). When given its broadest reasonable interpretation, this phrase relates merely to the intended result, after storing the claimed formulation or vial at 5°C for two months, that the remaining VEGF- antagonist protein content in native configuration (*e.g.*, not aggregated), constitutes “at least 98% of the VEGF antagonist” in the formulation or vial, measured using SEC. Even if given some limiting effect, the added phrase does not render the '992 Patent claims patentably distinct from the formulations and vials claimed in the OTDP Reference Patents for the reasons discussed below.

IV. IDENTIFICATION OF CLAIMS FOR WHICH REEXAMINATION IS REQUESTED AND IDENTIFICATION OF PRIOR ART THAT PRESENTS SUBSTANTIAL NEW QUESTIONS OF PATENTABILITY (37 C.F.R. § 1.510 (B)(2)-(3))

A. Claims for Which *Ex Parte* Reexamination is Requested and Identification of Prior Patents and Printed Publications

Reexamination of claims 1-18 (all claims) of the '992 Patent is requested in view of the commonly-owned OTDP Reference Patents, *i.e.*, the '261 Patent, the '594 Patent, and the '489 Patent. In accordance with 37 C.F.R. § 1.510(b)(3), a copy of every patent and printed publication relied upon or referred to in this Request is provided herewith and listed on the enclosed Form PTO/SB/08a.

1. **U.S. Patent No. 7,608,261 to Furfine et al. (“the ’261 Patent,” Exhibit 2)** was filed on June 14, 2007 and issued on October 27, 2009. Due to terminal disclaimers, the ’261 Patent will expire no later than March 7, 2021.
2. **U.S. Patent No. 9,340,594 to Furfine et al. (“the ’594 Patent,” Exhibit 3)** was filed on July 14, 2014 and issued on May 17, 2016. Due to terminal disclaimers, the ’594 Patent will expire no later than March 7, 2021.
3. **U.S. Patent No. 9,914,763 to Furfine et al. (“the ’763 Patent,” Exhibit 4)** was filed on April 11, 2016 and issued on March 13, 2018. Due to terminal disclaimers, the ’763 Patent will expire no later than March 7, 2021.
4. **U.S. Patent No. 10,400,025 to Furfine et al. (“the ’025 Patent,” Exhibit 5)** was filed on January 24, 2018 and issued on September 3, 2019. Due to terminal disclaimers, the ’025 Patent will expire no later than March 7, 2021.
5. **U.S. Patent No. 9,580,489 to Furfine et al. (“the ’489 Patent,” Exhibit 6)** was filed on May 11, 2016 and issued on February 28, 2017. Due to terminal disclaimers, the ’489 Patent will expire no later than March 7, 2021.
6. **PCT Publication No. WO 00/75319 A1 to Papadopoulos et al. (“Papadopoulos,” Exhibit 7)** published December 14, 2000 from PCT App. No. PCT/US00/14142. Papadopoulos and is prior art to the ’992 Patent under 35 U.S.C. § 102(b).
7. **U.S. Pub. No. 2016/0144025 A1 (the “Vitti Publication,” Exhibit 8)** published May 26, 2016 from U.S. App. No. 14/943,490. The Vitti Publication is not prior art to the ’992 Patent, but rather is included as evidence of Patent Owner’s admissions that the VEGF receptor-based fusion protein referred to in the prior art Papadopoulos reference as “VEGFR1R2-Fc Δ C1(a)” is aflibercept (Eylea®) and it is encoded by the amino acid sequence identically disclosed in the prior art Papadopoulos publication (Exhibit 7) and in SEQ ID NO: 4 of the ’992 Patent.
8. **PCT Publication No. WO 98/45331 A2 to Baca et al. (Exhibit 9)** published October 15, 1998 from PCT App. No. PCT/US98/06604. Baca et al. is prior art to the ’992 Patent under 35 U.S.C. § 102(b).

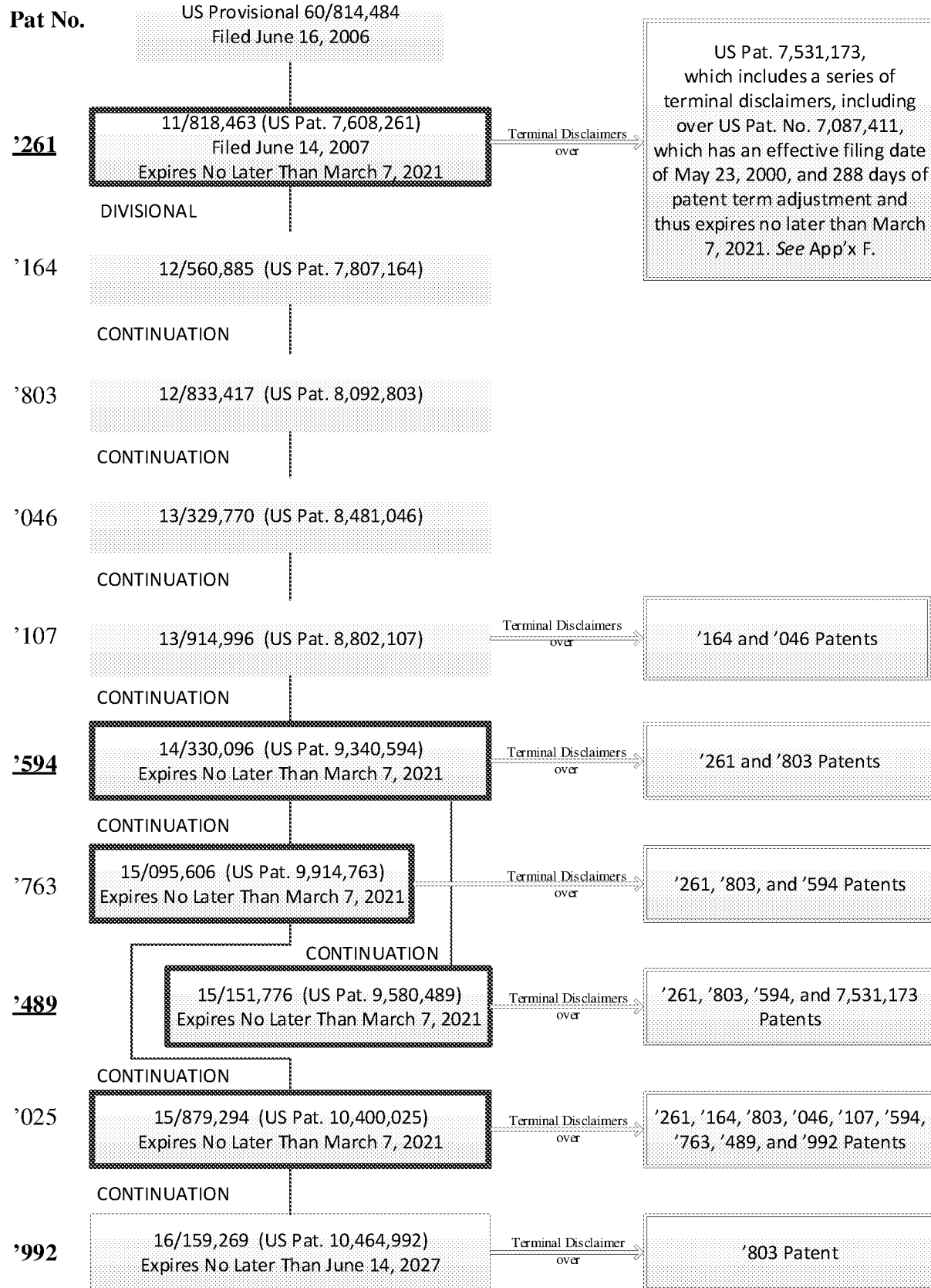
9. PCT Publication No. WO 00/63380 A1 to Cunningham et al. (Exhibit 10)

published October 26, 2000 from PCT App. No. PCT/US00/09483. Cunningham et al. is prior art to the '992 Patent under 35 U.S.C. § 102(b).

B. Each OTDP Reference Patent Expires Earlier than the '992 Patent

The '992 Patent claims priority through a series of applications (including all three OTDP Reference Patents) to U.S. Patent Application No. 11/818,463, filed June 14, 2007, which issued as the '261 Patent, and U.S. Provisional Application No. 60/814,484, filed June 16, 2006. During the '992 Patent's prosecution, Patent Owner filed a terminal disclaimer over U.S. Pat. No. 8,092,803, but not over any of the other patents in the Furfine Family, as depicted below:

REQUEST FOR *EX PARTE* REEXAMINATION OF U.S. PATENT NO. 10,464,992



The challenged '992 Patent and all of the other patents in the Furfine Family claim priority to the '261 Patent and the same provisional application filed on June 16, 2006. Due to a series of terminal disclaimers, the '261 Patent expires no later than March 7, 2021. *See* Appendix F. The other OTDP Reference Patents are both terminally disclaimed over at least the '261 Patent, and therefore also expire no later than March 7, 2021. The OTDP Reference Patents are appropriate as obviousness-type double patenting references because they expire at least six years earlier than the '992 Patent. *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust*, 764 F.3d 1366, 1374 (Fed. Cir. 2014) (“[T]he doctrine of obviousness-type double patenting continues to apply where two patents that claim the same invention have different expiration dates.”); *Gilead Scis., Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1215 (Fed. Cir. 2014).

V. STATEMENT POINTING OUT EACH SUBSTANTIAL NEW QUESTION OF PATENTABILITY (37 C.F.R. § 1.510(B)(1))

Requester submits that substantial new questions (“SNQ”) of patentability exist with respect to all claims of the '992 Patent (claims 1-18) and requests *ex parte* reexamination of those claims based at least on the substantial new questions summarized below:

- SNQ1.** Claims 1-18 of the '992 Patent are unpatentable on grounds of obviousness-type double patenting over claims 1-5 of the '594 Patent, optionally in view of Papadopoulos and the Exemplary Vial Pubs.;
- SNQ2.** Claims 1-18 of the '992 Patent are unpatentable on grounds of obviousness-type double patenting over claims 1-5 of the '261 Patent, optionally in view of Papadopoulos and the Exemplary Vial Pubs.;
- SNQ3.** Claims 1-18 of the '992 Patent are unpatentable on grounds of obviousness-type double patenting over claims 1-29 of the '489 Patent, optionally in view of Papadopoulos.

To establish a substantial new question of patentability, the request must demonstrate that

the patent or prior art relied upon in a proposed rejection “presents a new, non-cumulative technological teaching that was not previously considered and discussed on the record during the prosecution of the application that resulted in the patent for which reexamination is requested.” MPEP § 2216. However, “[t]he substantial new question of patentability may be based on art previously considered by the Office if the reference is presented in a new light or a different way that escaped review during earlier examination.” *Id.*; 35 U.S.C. § 303(a) (“The existence of a substantial new question of patentability is not precluded by the fact that a patent or printed publication was previously cited by or to the Office or considered by the Office.”). “A double patenting issue may raise a substantial new question of patentability of a claim of a patent, and thus can be addressed in a reexamination proceeding.” MPEP § 804(I)(D).

A substantial new question of patentability exists based on obviousness-type double patenting over the earlier-expiring ’261 and ’594 Patents, because the Examiner incorrectly concluded that the stability result language rendered the claims of the ’992 Patent patentably distinct from the claims of these earlier-expiring patents. It does not. Assuming *arguendo* that the stability result language is considered to be a limitation, this Request demonstrates—based on Patent Owner’s own data reported in the specification common to the ’992 Patent and each of the OTDP Reference Patents (the “Common Specification”)—that the formulations claimed in ’261 and ’594 Patents inherently achieve the stability result claimed in the ’992 Patent. The work of the inventor or the patent itself can be used as the evidence of inherency. *See, e.g., Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) (analyzing inherency based on the disclosure of the “patent itself”).

It is well-settled that claiming an inherent property of a composition does not render a claim to the composition nonobvious. *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d

1322, 1332-33 (Fed. Cir. 2020) (holding patent invalid as obvious because it “simply recites a composition, with a ‘wherein’ clause that describes the stability of that recited composition, a result that was inherent in the prior art.”). *See also Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (“[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer.” (citing *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985))).

A patent can be invalid based on inherency when the patent itself makes clear that a limitation is “not an additional requirement imposed by the claims ..., but rather a property necessarily present.” *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009); *see also Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1191 (Fed. Cir. 2019) (“[T]he district court did not err by finding that the pharmacokinetic limitations of the asserted claims were inherent and added no patentable weight to the pharmacokinetic claims.”); *Alcon Research*, 687 F.3d at 1369 (“[T]his claim language does not impose any additional requirement because the ’805 patent itself defines mast cell stabilization as a property that is necessarily present at those concentrations.”).

This Request thus presents the ’261 and ’594 Patents in a “new light” and in a different way that escaped review during earlier examination. By explaining the import of the experimental results reported in the Common Specification, this request also presents new, non-cumulative technological teachings that were not previously considered and discussed on the record during the prosecution of the application that resulted in the ’992 Patent.

The ’261 and ’594 Patents claim very specific formulations that 1) fall within the genus of formulations claimed in the ’992 Patent, and 2) are reported in the Common Specification as

achieving the claimed stability result. Specifically, as explained in detail below, claim 5 of the '261 Patent, and claim 5 of the '594 Patent, each recite the same VEGF specific fusion protein of SEQ ID NO: 4, in a formulation with specific combinations of the organic co-solvent, buffer, stabilizing agent(s), and pH that is disclosed in Examples 3 and 4 of the Common Specification as resulting in greater than 99% of the VEGF antagonist in native conformation following storage at 5°C for two months as measured by SEC. Thus, claims 1-18 of the '992 patent are anticipated by, or at the very least are obvious variants of, the claims of each of the '261 Patent and the '594 Patent. Insertion of a stability result did not render the formulation claimed in the '992 Patent patentably distinct from more specific formulations claimed in the earlier-expiring '261 and '594 Patents. Therefore, the Examiner erred in withdrawing the obviousness-type double patenting rejections over each of the '261 Patent and the '594 Patent, and this Request demonstrates a substantial new question of patentability by presenting these references in a new light.

A substantial new question of patentability also exists based on obviousness-type double patenting over the '489 Patent. The '489 Patent was not cited or discussed during prosecution of the application that became the '992 Patent. The '489 Patent presents a new, non-cumulative technological teaching because it claims a formulation and vial containing the same VEGF antagonist fusion proteins produced in CHO cells, buffer, organic co-solvent, and stabilizing agent as the '992 Patent, and also recites that “at least 90% of the total weight of the VEGF-specific fusion protein antagonist is not present as an aggregate.” As explained in detail below, the claims of the '489 Patent as a whole render obvious the same formulation of Examples 3 and 4 of the Common Specification, which achieves the result of greater than 99% of the same VEGF antagonist in native conformation after two months of storage. *See* Section VI.F. *infra*.

The '489 Patent therefore presents a substantial new question of patentability because the Examiner 1) did not cite the '489 Patent and all, and 2) did not recognize that the experimental results presented in the Common Specification demonstrate that the '489 Patent claims cover the same formulations and stability result claimed in the '992 Patent.

The Examiner did not cite or discuss Papadopoulos during prosecution of the '992 Patent. Papadopoulos teaches that the VEGF antagonist fusion protein of SEQ ID NO: 4 and its production in CHO cells were known in the prior art. The claims of any of the OTDP Reference Patents in view of Papadopoulos present a substantial new question of patentability because it supports the obviousness of the subject matter claimed in the '992 Patent over the claims of each of the OTDP Reference Patents. In particular, Papadopoulos presents a new technological teaching demonstrating that claiming production of the fusion proteins "in a Chinese Hamster Ovary (CHO) cell" does not patentably distinguish the claims of the '992 Patent over the earlier-expiring OTDP Reference Patents.

A substantial new question of patentability therefore exists based on obviousness-type double patenting over each of the '261, '594, and '489 Patents, optionally in combination with Papadopoulos.

VI. SUBSTANTIAL NEW QUESTIONS OF PATENTABILITY AND DETAILED DISCUSSION OF HOW THE CITED ART IS APPLIED TO THE CHALLENGED CLAIMS (37 C.F.R. § 1.510(b)(2))

In accordance with 37 C.F.R. §§ 1.510 (b)(1) and (2), the following sections provide a detailed explanation about how the OTDP Reference Patents are being applied to the challenged claims 1-18. Further detailed explanations of how each reference patent renders the claims of the '992 Patent unpatentable for obviousness-type double patenting are presented in the claim charts attached hereto as Appendices A-C.

A. Obviousness-Type Double Patenting is an Appropriate Basis for Reexamination of the '992 Patent

The '992 Patent, with an expiration date over six years after the OTDP reference patents, provides an unjustified timewise extension of Patent Owner's monopoly. Nonstatutory obviousness-type double patenting may raise substantial new questions of patentability, and is an appropriate basis for instituting *ex parte* reexamination. MPEP § 2258(I)(D) ("[T]he issue of double patenting, over prior art patents or non-prior art patents, is appropriate for consideration in reexamination under 35 U.S.C. § 302, both as a basis for ordering reexamination under 35 U.S.C. § 304 and during subsequent examination on the merits."); *see, e.g., In re Janssen Biotech, Inc.*, 880 F.3d 1315, 1317-18 (Fed. Cir. 2018) (affirming decision in an *ex parte* reexamination that held claims unpatentable for obviousness-type double patenting); *In re Lonardo*, 119 F.3d 960, 966 (Fed. Cir. 1997).

"The ban on double patenting ensures that the public gets the benefit of the invention after the original period of monopoly expires.... It is designed to prevent an inventor from securing a second, later expiring patent for the same invention." *AbbVie Inc.*, 764 F.3d at 1373. An inventor also cannot avoid the double patenting doctrine by procuring a later-expiring patent containing only small differences from the earlier-expiring patent. Rather, "it is a bedrock principle of our patent system that when a patent expires, the public is free to use not only the same invention claimed in the expired patent but also obvious or patentably indistinct modifications of that invention." *Gilead Scis., Inc.*, 753 F.3d at 1214. "[T]hat principle is violated when a patent expires and the public is nevertheless barred from practicing obvious modifications of the invention claimed in that patent because the inventor holds another later-expiring patent with claims for obvious modifications of the invention." *Id.* "Thus, if the later expiring patent is 'merely an obvious variation of an invention disclosed and claimed in the

[reference] patent,’ the later expiring patent is invalid for obviousness-type double patenting.” *AbbVie Inc.*, 764 F.3d at 1379 (quoting *In re Vogel*, 422 F.2d 438, 441 (CCPA 1970)).

Secondary considerations of nonobviousness, such as unexpectedly superior results, are not considered in the context of obviousness-type double patenting. *See Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 999 (Fed. Cir. 2009); *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1377 n.1 (Fed. Cir. 2003) (“Obviousness requires inquiry into objective criteria suggesting non-obviousness; nonstatutory double patenting does not.”).

The Federal Circuit has made clear that, even for post-URAA patents, “obviousness-type double patenting continues to apply where two patents that claim the same invention have different expiration dates.” *AbbVie Inc.*, 764 F.3d at 1374. Nonstatutory double patenting rejections are appropriate where, as here, “the applicant chooses to file separate applications for overlapping subject matter,” thereby obtaining different expiration dates. *Id.* at 1373.

Here, Patent Owner obtained issuance of the OTDP Reference Patents by filing terminal disclaimers such that those patents expire no later than March 7, 2021. *See* Section IV.B. *supra*. That expiration date is part of the bargain with the public by which Patent Owner obtained the OTDP Reference Patents, and cannot be withdrawn. *See In re Yamazaki*, 702 F.3d 1327, 1332-34 (Fed. Cir. 2012) ; MPEP § 1490(VIII)(B) (“The mechanisms to correct a patent ... are not available to withdraw or otherwise nullify the effect of a recorded terminal disclaimer. As a general principle, public policy does not favor the restoration to the Patent Owner of something that has been freely dedicated to the public.”).

The ’992 Patent provides an unjustified timewise extension of Patent Owner’s monopoly by broadly claiming formulations that are anticipated or obvious over the claims of the earlier-expiring OTDP Reference Patents. The ’992 Patent claims should therefore be rejected for

double patenting. *See AbbVie Inc.*, 764 F.3d at 1373 (“[T]he doctrine of obviousness-type double patenting ensures that a particular invention (and obvious variations thereof) does not receive an undue patent term extension.”).

B. A One-Way Obviousness Type Double Patenting Test Applies

MPEP § 804 explains that nonstatutory double patenting includes rejections based on anticipation, one-way or two-way determinations of obviousness, and rejections based on the equitable principle against permitting an unjustified timewise extension of patent rights. “If the application under examination is the later-filed application, or both applications are filed on the same day, only a one-way determination of distinctness is needed in resolving the issue of double patenting, *i.e.*, whether the invention claimed in the application would have been anticipated by, or an obvious variation of, the invention claimed in the patent.” MPEP § 804(II)(B)(2)(b). “If a claimed invention in the application would have been obvious over a claimed invention in the patent, there would be an unjustified timewise extension of the patent and a nonstatutory double patenting rejection is proper.” *Id.*

Here, the ’992 Patent and each of the OTDP Reference Patents claim priority to a common parent application, filed June 16, 2006. The specifications of these patents are substantially identical and, with respect to the disclosures relevant to the claims at issue, are identical. Therefore, because the applications that issued as these patents were filed on the same day (by virtue of their common parent application), or because the claims of the ’992 Patent could have been filed in each of the earlier-issued patents (by virtue of their nearly identical disclosures), a one-way test is appropriate.

C. 35 U.S.C. § 121 Does Not Prevent Using Any of the OTDP Reference Patents as the Basis for Double Patenting Rejections

The Safe Harbor provision of 35 U.S.C. § 121 only protects applicants from obviousness-

type double patenting invalidity when they are forced to pursue inventions in separate patent applications as a result of a restriction requirement set by the USPTO. *See Geneva Pharms., Inc.*, 349 F.3d at 1378-79. “Given the potential windfall [a] patent term extension could provide to a patentee,” the courts apply a “strict test for application of §121.” *Id.* at 1382. The Federal Circuit has established three requirements for invoking the protection of the Safe Harbor provision: (1) a restriction requirement, (2) a divisional application filed as a result of the restriction requirement, and (3) consonance with the restriction requirement. *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1579 (Fed. Cir. 1991).

The consonance requirement prevents an applicant from reclaiming, through a divisional application, the invention that was elected and examined in the parent.

Consonance requires that the line of demarcation between the ‘independent and distinct inventions’ that prompted the restriction requirement be maintained. Though the claims may be amended, *they must not be so amended as to bring them back over the line imposed in the restriction requirement*. Where that line is crossed the prohibition of the third sentence of Section 121 does not apply.

Id. (quoting *Gerber Garment Tech., Inc. v. Lectra Sys., Inc.*, 916 F.2d 683, 688 (Fed. Cir. 1990) (emphasis added)). In other words, the Safe Harbor provision does not apply when an application claims the same invention that was elected for prosecution in the parent application.

The OTDP Reference Patents are all members of the same Furfine patent family as the ’992 Patent. *See* chart in Section IV.B. *supra*. A restriction requirement was issued during pendency of the ’261 Patent application, requiring the applicant to elect between (a) formulation claims and (b) method claims directed to methods of making a lyophilized formulation. The applicant elected to prosecute the formulation claims, which issued as the ’261 Patent. Applicant then pursued a divisional with the method claims, which issued as the ’164 Patent.

The '992 Patent is part of a chain of continuation applications filed from the '164 divisional application, and is a continuation of each of the other OTDP Reference Patents. To benefit from the Safe Harbor provision of 35 U.S.C. §121, the '992 Patent must maintain consonance with the original restriction requirement (*i.e.*, by pursuing only the method claims that were restricted from the '261 Patent). *See Symbol Techs., Inc.*, 935 F.2d at 1579.

Here, the '992 Patent claims clearly crossed the “line of demarcation” set by the restriction requirement because both the '992 Patent and the '261 Patent recite claims directed to the same formulations. The '992 Patent therefore is not entitled to the Safe Harbor provision of 35 U.S.C. § 121 for obviousness-type double patenting rejections over the '261 Patent. *See* MPEP § 804.01.

The '992 patent is a continuation of each of the '594 and '489 Patents, and therefore is not eligible for the Safe Harbor of § 121. Moreover, each of the '594 and '489 Patents, like the '261 and '992 patents, claims formulations rather than the restricted methods.

D. SNQ1: Claims 1–5 of the '594 Patent Create a Substantial New Question of Patentability Based on Obviousness-Type Double Patenting

Claims 1-18 of the '992 Patent are unpatentable over claims 1-5 of the '594 Patent for obviousness-type double patenting. Claim 5 of the '594 Patent (including the claims from which it depends) recites a specific formulation that falls within the scope of every claim of the '992 Patent, and the Common Specification demonstrates that this claimed formulation achieves the exact result that the Patent Owner used to overcome the examiner's double patenting rejection. In addition to the discussion below, a detailed explanation of how the '594 patent renders the claims of the '992 patent unpatentable for obviousness-type double patenting is presented in the claim chart attached hereto as Appendix A.

1. Independent Claims 1 and 10 are Unpatentable For Double Patenting Over the '594 Patent

The first step in the obviousness-type double patenting analysis is to compare the later-expiring claims to the earlier-expiring claims. *See AbbVie Inc.*, 764 F.3d at 1374. The second step is to determine whether those differences render the claims patentably distinct. “‘A later claim that is not patentably distinct from,’ *i.e.* ‘is obvious over[] or anticipated by,’ an earlier claim is invalid for obviousness-type double patenting.” *Id.* (quoting *Eli Lilly*, 251 F.3d at 968).

Claim 1 of the '992 Patent recites:

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 immunoglobulin-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.

Claim 10 is identical to claim 1 except the word “vial” in the preamble is substituted with the word “formulation.” Thus, claims 1 and 10 are discussed together below.

As explained in Section II.C., during prosecution, Patent Owner did not dispute that the '594 Patent claims contained each of the components of the claimed vial and formulation, *i.e.*, the claimed VEGF antagonist, an organic co-solvent, a buffer, and a stabilizing agent. Rather, in

response to the Examiner’s obviousness-type double patenting rejection, Patent Owner amended the claims to recite the stability test results from the specification’s examples and argued that those test results were not in the ’594 Patent’s claims. The phrase “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,” only states an intended result and is therefore non-limiting. *See, e.g., In re Copaxone Consol. Cases*, 906 F.3d at 1023. Nonetheless, even if this phrase is given patentable weight, it does not render the claims of the ’992 Patent patentably distinct from the claims of the ’594 Patent because the Common Specification itself demonstrates that the formulations claimed in the ’594 Patent inherently achieve this level of stability.

a. The ’594 Patent Claims a Species Within the Scope of the ’992 Patent Claims

The table below shows that the independent claims of the ’992 Patent (claims 1 and 10) are not patentably distinct from claim 5 of the ’594 Patent:

’992 Patent Independent Claims (Claims 1 and 10)	’594 Patent, Claim 5, which depends from claims 4, 3, 2, and 1
A vial [or formulation] comprising: a vascular endothelial growth factor (VEGF) antagonist,	’594 Patent, claim 1: “A pre-filled syringe suitable for intravitreal administration comprising a 1 mL luer glass syringe fitted with a plunger and a stable ophthalmic formulation of a vascular endothelial growth factor (VEGF) trap...” It was known to store protein formulations in a vial. <i>See, e.g., Exemplary Vial Pubs.</i> (Ex. 9, 47:14-18; Ex. 10, 25:20-27).
an organic co-solvent	’594 Patent, claim 5: “The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF trap,

	10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20 , 5% sucrose, at pH 6.2-6.4.”
a buffer	’594 Patent, claim 5: “The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF trap, 10 mM phosphate , 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, at pH 6.2-6.4.”
a stabilizing agent	’594 Patent, claim 5: “The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF trap, 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose , at pH 6.2-6.4.”
wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and	’594 Patent, claim 1: “A...a vascular endothelial growth factor (VEGF) trap, which consists of (i) a receptor component consisting essentially of an immunoglobulin-like domain 2 of a first VEGF receptor and an immunoglobulin-like domain 3 of a second VEGF receptor, and (ii) a multimerizing component” ’594 Patent, claim 4: “wherein the VEGF trap consists of amino acids 27-457 of SEQ ID NO:4 .” Papadopoulos at 26:14-17 discloses that Regeneron’s VEGF trap molecules, including VEGFR1R2-FcΔC1(a) (aflibercept, SEQ ID NO:4), were produced in CHO cells .
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.	’594 Patent, claim 3: “The pre-filled syringe according to claim 2, wherein the VEGF trap is stable for at least 4 months .” Examples 3 and 4 of the Common Specification evidence the inherent stability results for the formulation of claim 5.

As shown in the chart above, claim 5 of the '594 patent recites a specific formulation that falls within the broader genus claims of the '992 patent, and therefore anticipates the '992 Patent claims. As noted in Section II.A., the '992 Patent specification states that polysorbate 20 is an “organic co-solvent,” 10 mM phosphate is a “buffer,” and sucrose is a “stabilizing agent.” '992 Patent, col. 2:25-38. A claim in a reference patent that recites a “species renders the later genus claims invalid under non-statutory double patenting.” *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1374 (Fed. Cir. 2005); *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 971 (Fed. Cir. 2001) (“[Federal Circuit] case law firmly establishes that a later genus claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim.”). That is the case here. The formulation claimed in claim 5 the '594 Patent is a species of the broad formulation claimed in the '992 Patent, rendering claims 1 and 10 of the '992 invalid for double patenting.

Moreover, as demonstrated below, the formulation recited in claim 5 of the '594 Patent achieves the same stability result claimed in the '992 Patent.

b. The '594 Patent Claims Meet the Stability Recited in the '992 Patent's “Wherein” Clause, Expressly or Inherently

Claim 3 of the '594 Patent (from which claim 5 depends) expressly recites that the VEGF trap (*i.e.*, VEGF antagonist fusion protein) “is stable for at least 4 months.” '594 Patent, claim 3, 1:36-48 (stating that the VEGF-specific fusion protein antagonist is also referred to as a VEGF “trap”). It is appropriate to look to the specification of the reference patent to determine the scope and meaning of the claims of an obviousness-type double patenting reference, and “when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the reference patent or application.” MPEP § 804(II)(B)(2)(a).

The '594 Patent does not define the term “stable,” but states that “stability is determined

in a number of ways at specified time points, including ... size exclusion HPLC.” *Id.* at 6:42-48, 8:2-3 (“Stability was determined by SE-HPLC,” *i.e.*, size exclusion chromatography (SEC)). A POSA reading the ’594 Patent would understand that a “stable” formulation retains a very high percentage of the protein in “native configuration” following storage, as measured by SEC, based on the data reported for all of the example formulations. *See id.* at Tables 1-8. Claim 3 recites that the protein “is stable” for *at least four months*, and therefore anticipates or renders obvious the ’992 Patent claims’ requirement 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.”

Moreover, the Common Specification evidences that the specific formulation recited in claim 5 of the ’594 Patent inherently achieves the result recited in the ’992 Patent’s “wherein” clause. Claim 5 of the ’594 Patent specifically covers the formulation tested in Examples 3 and 4 of the Common Specification:

Examples 3 & 4 of the Common Specification	’594 Patent, Claim 5, which depends from claims 4, 3, 2, and 1
40 mg/ml VEGF Trap	“40 mg/mL of the VEGF Trap,” (claim 5) “wherein the VEGF trap consists of amino acids 27-457 of SEQ ID NO: 4” (claim 4)
10 mM phosphate	10 mM phosphate
40 mM NaCl	40 mM NaCl
0.03% polysorbate 20	0.03% polysorbate 20
5% sucrose	5% sucrose
pH 6.3	pH 6.2-6.4

Example 3 of the Common Specification evidences the inherent stability results for the composition of claim 5 of the ’594 Patent when stored in glass vials. Example 3 discloses that “[a] liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 40

mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5°C in 3 ml glass vials and samples tested at 0.5, 1, 2, 3, and 4 months” and showed by SEC that the formulation has **99.2%** of the VEGF trap in native conformation at two months. *See* Table 3 of the ’992 Patent.

Example 4 of the Common Specification evidences the inherent stability results for the composition of claim 5 when stored in glass syringes. Example 4 discloses that “[a] liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO: 4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5°C. in 1 ml prefilled luer glass syringe ... and samples tested at 0.5, 1, 2, 3, and 4 months” and showed by SEC that the formulation has **99.1%** of the VEGF trap in native conformation at two months. *See* Table 4 of the ’992 Patent.

The “VEGF trap (SEQ ID NO:4)” of Examples 3 and 4 is the same fusion protein that “consists of amino acids 27-457 of SEQ ID NO:4,” recited in claim 4 of the ’594 Patent, *i.e.*, aflibercept. *See* Section II.B. *supra*; Ex. 8 ¶¶ [0086], [0197].

Thus, the formulation claimed in the ’594 Patent inherently achieves stability such 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,” regardless of whether it is stored in a vial or a syringe. In now claiming, in the ’992 Patent, the stability results achieved when storing the previously patented formulation, Patent Owner has merely claimed an inherent result or property of the formulation of claim 5 of the ’594 Patent. This does not distinguish the new claims over Patent Owner’s existing, earlier-expiring claims. *See, e.g., In re Crish*, 393 F.3d 1253, 1258 (Fed. Cir. 2004) (“A long line of cases confirms that one cannot establish novelty by claiming a known material by its properties.”); *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990) (“The discovery of a new property or use of a previously known composition, even

when that property and use are unobvious from prior art, can not impart patentability to claims to the known composition.”). *See also In re Burke*, Appeal No. 2012-012640, 2015 WL 5782989, at *6 (PTAB Sept. 16, 2015) (affirming double patenting rejection where the reference patent claimed the same elements except the inherent result claimed in the application).

c. The Claims are Not Made Patentably Distinct by Reciting that the VEGF Antagonist is “Produced in” CHO Cells

The phrase “wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell” in the ’992 Patent claims is a product-by-process limitation. “[P]atentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) (citation omitted); MPEP § 2113. There is no indication here that the claimed fusion protein “produced in a [CHO] cell” is any different from the fusion protein claimed in the ’594 Patent. To the contrary, the ’992 Patent and the ’594 Patent have the same specification and support for this process element. The ’594 Patent specification thus discloses that its claimed VEGF antagonist fusion protein can be “expressed in a mammalian cell line such as a CHO cell.” ’594 Patent, 6:2-4. For at least this reason, the recitation of production in CHO cells does not render the ’992 Patent claims patentably distinct over the ’594 Patent claims.

Moreover, it was entirely obvious to produce the VEGF fusion protein recited in the claims of the ’594 Patent in CHO cells. Papadopoulos taught detailed processes for production of Patent Owner’s VEGF antagonists in CHO cells. *See, e.g.* Ex. 7, 12:19-26, 67:25 – 68:5. Papadopoulos specifically reports that the protein of SEQ ID NO: 4 claimed in the ’594 Patent (*i.e.*, “VEGFR1R2-FcΔC1(a)”) was expressed in CHO cells. *Id.* at 82:12-13. Thus, the claims of the ’594 Patent, at least in view of Papadopoulos, render claims 1 and 10 of the ’992 Patent

invalid for obviousness-type double patenting.

Additionally, other members of the Furfine Family also claim the same VEGF antagonists produced in CHO cells. *See* '489 Patent, claim 24 ("The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist is expressed in a Chinese hamster ovary (CHO) cell."); '763 Patent, claims 1 and 12 ("wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell"). No restriction requirement was issued during prosecution of either the '489 or '763 Patent, which indicates that recitation of production in CHO cells does not render these claims patentably distinct from claims omitting production in CHO cells.

The VEGF antagonist protein in the product-by-process claim of the '992 Patent is the same as or obvious over the VEGF antagonist protein claimed in the OTDP Reference Patents both because (1) the '594 Patent teaches that the VEGF antagonist protein was produced in CHO cells, and (2) it was known from Papadopoulos that the same VEGF antagonist protein was produced in CHO cells.

d. The Claims are Not Made Patentably Distinct by Reciting a "Vial"

It would have been obvious for a POSA to place the formulation claimed in the '594 Patent in a vial, because a vial is a well-known standard container for a pharmaceutical formulation. The recitation of a vial in independent claim 1 of the '992 Patent does not create a patentable distinction over the '594 patent claims. This is evidenced by the fact that Patent Owner has previously patented both "a formulation" and "a vial" containing VEGF antagonist formulations together in the '489 Patent (as well as the '992 Patent itself), without any requirement for restriction between claims to a vial and claims to a formulation. *See* Section VI.F. *infra*, '489 Patent, claim 26 ("A vial containing a formulation comprising: (a) 1-100 mg/mL of a VEGF-specific fusion protein antagonist"). Thus, there is no basis to conclude that

claims directed to a vial comprising a formulation are patentably distinct from claims to a formulation in general.

Moreover, it was well known in the prior art to contain VEGF antagonist formulations in vials, as evidenced by the Exemplary Vial Pubs. *See, e.g.*, Ex. 9 (WO 98/45331), 47:14-18; Ex. 10 (WO 00/63380), 25:20-27. Thus, at a minimum, the claims of the '594 Patent in view of the Exemplary Vial Pubs render claim 1 invalid for obviousness-type double patenting.

e. Claims 1 and 10 as a Whole are Unpatentable

In sum, claims 1-5 of the '594 Patent recite a specific formulation that falls within the genus of formulations claimed in claims 1 and 10 of the '992 Patent, and therefore anticipate or render obvious the '992 Patent claims. Neither the recitation of production in CHO cells, nor that the formulation is in a vial, lends patentability to the claims. Critically, the Common Specification itself demonstrates that the formulation claimed in claims 1-5 of the '594 Patent inherently achieves the stability limitation recited in the '992 Patent's "wherein" clause. The technological teachings discussed above were not previously considered and discussed on the record during the prosecution of the application that resulted in the '992 Patent. This request presents the reference '594 Patent in a "new light" and in a different way that escaped review during earlier examination, and therefore presents a substantial new question of patentability. The Examiner erred by not maintaining the obviousness-type double patenting rejection over the '594 Patent.

The claims of the '992 Patent were not rendered patentably distinct from the claims of the '594 Patent by Patent Owner's insertion of an intended result. The '992 Patent's formulation "cannot become nonobvious simply by ... claiming the [result].... To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344,

1354 (Fed. Cir. 2012). In the '992 patent, Patent Owner has attempted to extend the term of exclusivity it has under the '594 patent by obtaining new claims to essentially the same subject matter. “Effectively extending the patent term, however, is precisely the result that the doctrine of obviousness-type double patenting was created to prevent.” *In re Berg*, 140 F.3d 1428, 1435 (Fed. Cir. 1998). Therefore, because independent claims 1 and 10 are anticipated by or obvious variants of claims 1-5 of the '594 Patent, claims 1 and 10 are unpatentable for obviousness-type double patenting.

2. Dependent Claims 2 and 11 are Unpatentable For Double Patenting Over the '594 Patent

Dependent claim 2 of the '992 Patent recites:

The vial of claim 1, wherein about 99% or more of the weight of the fusion protein is in native conformation.

Claim 11 is identical to claim 2 except the word “vial” in the preamble is substituted with the word “formulation” and it depends from claim 10. Thus, claims 2 and 11 are discussed together below. Requester incorporates the explanations provided above for claims 1 and 10 in Section VI.D.1. above.

The same examples discussed above evidence that formulations claimed in claims 1–5 of the '594 Patent had “99% or more of the weight of the fusion protein ... in native conformation,” as recited in claims 2 and 11 of the '992 Patent. To the extent that this intended result is given patentable weight, it is an inherent result of the formulation claimed in the '594 Patent.

Examples 3-4 of the Common Specification show that the formulation of claims 1-5 of the '594 Patent had 99.1% and 99.2% of the weight of the fusion protein in native conformation following storage for two months at 5°C, when stored in syringes and vials, respectively. Therefore, the Examiner erred by not maintaining the obviousness-type double patenting rejection. The claims

of the '992 Patent were not rendered patentably distinct from the claims of the '594 Patent by Patent Owner's insertion of this result into the claims. Thus, because claims 2 and 11 are anticipated by or obvious variants of claims 1-5 of the '594 Patent, claims 2 and 11 are unpatentable for obviousness-type double patenting.

3. Dependent Claims 3, 4, 12 and 13 are Unpatentable For Double Patenting Over the '594 Patent

Dependent claim 3 of the '992 Patent recites:

The vial of claim 1, 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.

Dependent claim 4 of the '992 Patent recites:

The vial of claim 3, wherein the fusion protein comprises amino acids 27-457 of SEQ ID NO:4.

Claims 12 and 13 are identical to claims 3 and 4, respectively, except the word "vial" in the preamble is substituted with the word "formulation" and the latter claims depend from independent claim 10. Requester incorporates the explanations provided above for claims 1 and 10 in Section VI.D.1. above.

Claim 4 of the '594 Patent recites that "the VEGF trap consists of amino acids 27-457 of SEQ ID NO:4." SEQ ID NO: 4 of the '594 Patent is identical to SEQ ID NO: 4 of the '992 Patent, as the two patents share the Common Specification. Therefore, claim 4 of the '594 Patent (from which claim 5 depends) recites a species of fusion protein that anticipates the genus "VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and the human Flt4" of claims 3 and 12 of the '992 Patent, as well as the fusion protein comprising amino acids 27-457 of SEQ ID NO:4 recited in claims 4 and 13 of the '992 Patent. The claims are not patentably distinct.

The Examiner therefore erred by not maintaining the obviousness-type double patenting rejection. Because claims 3, 4, 12 and 13 are anticipated by or obvious variants of claims 1-5 of the '594 Patent, these claims are unpatentable for obviousness-type double patenting.

4. Dependent Claims 5 and 14 are Unpatentable For Double Patenting Over the '594 Patent

Dependent claim 5 of the '992 Patent recites:

The vial of claim 4, wherein the VEGF antagonist is a dimer of the fusion protein.

Claim 14 is identical to claim 5 except the word “vial” in the preamble is substituted with the word “formulation” and it depends on independent claim 10. Requester incorporates the explanations provided above for claims 1 and 10 in Section VI.D.1. above.

The recitation that the VEGF antagonists is a dimer is not a patentable distinction, as this is merely a property of the VEGF antagonist claimed in the '594 Patent and known in the prior art. The VEGF antagonist of SEQ ID NO: 4 (aflibercept) comprises the Fc region of human IgG as a “multimerizing component,” and is known to exist as a dimer. '594 Patent (SEQ ID NO:4); Ex. 8 ¶¶ [0086], [0197] (confirming that aflibercept “consists of a dimer of two polypeptides consisting of amino acids 27-457”). The '594 Patent discloses that “the VEGF antagonist is a dimer composed of two fusion proteins of SEQ ID NO:4.” '594 Patent, 6:7-8. The prior art Papadopolous reference also discloses that the VEGF trap molecules form dimers. Ex. 7 at 70:23-24 (confirming the closely related VEGF trap “Flt1D2.Flk1D3.FcC1(a)” of SEQ ID NO:2 is a “dimer”); *see also* 12:10, 25:23-35 (noting intermolecular disulfide bonds in the Fc region); Fig 24B-C (identifying the Fc region in the aflibercept sequence).

Therefore, the Examiner erred by not maintaining the obviousness-type double patenting rejection. The claims of the '992 Patent were not rendered patentably distinct from the claims of

the '594 Patent by Patent Owner's insertion of an intended result. Thus, because claims 5 and 14 are anticipated by or obvious variants of claims 1-5 of the '594 Patent, claims 5 and 14 are unpatentable for obviousness-type double patenting.

5. Dependent Claims 6-9 and 15-18 are Unpatentable For Double Patenting Over the '594 Patent

Dependent claims 6-9 and 15-18 encompass a formulation comprising polysorbate 20, sucrose, and/or phosphate buffer, in various combinations. Claim 6 of the '992 Patent recites:

The vial of claim 5, wherein the organic co-solvent is selected for the group consisting of **polysorbate 20**, polysorbate 90, polyethylene glycol (PEG), PEG3350, and propylene glycol.

Claim 7 of the '992 Patent recites:

The vial of claim 6, wherein the stabilizing agent is selected from the group consisting of **sucrose**, sorbitol, glycerol, trehalose, and mannitol.

Claim 8 of the '992 Patent recites:

The vial of claim 1, wherein the organic co-solvent is **polysorbate 20** and the stabilizing agent is **sucrose**.

Claim 9 of the '992 Patent recites:

The vial of claim 1, wherein the organic co-solvent is **polysorbate 20**, the buffer is **phosphate**, and the stabilizing agent is **sucrose**.

Claims 15–18 are identical to claims 6–9, respectively, except the word “vial” in the preamble is substituted with the word “formulation” and claims 15–18 ultimately depend from claim 10. Requester incorporates the explanations provided above for claims 1 and 10 in Section VI.D.1. above.

Claim 5 of the '594 Patent recites, in a single formulation, the same elements as claims 6-9 and 15-18 of the '992 Patent, *i.e.*, “ **10 mM phosphate**, 40 mM NaCl, 0.03% **polysorbate 20**,

5% **sucrose**.” Claim 5 therefore anticipates, or at a minimum renders obvious, the subject matter of claims 6–9 and 15–18 of the ’992 Patent. This is the same formulation that inherently achieves the results recited in the “wherein” clauses of claims 1, 2, 10 and 11 of the ’992 Patent. *See* Sections VI.D.1.b. and VI.D.2. *supra*. Claims 6–9 and 15–18 of the ’992 Patent are not patentably distinct over the ’594 Patent claims.

Therefore, the Examiner erred by not maintaining the obviousness-type double patenting rejection. The claims of the ’992 Patent were not rendered patentably distinct from the claims of the ’594 Patent by Patent Owner’s insertion of an intended result. Thus, because claims 6–9 and 15–18 are anticipated by or obvious variants of claims 1-5 of the ’594 Patent, these claims are unpatentable for obviousness-type double patenting.

E. SNQ2: Claims 1-5 of the ’261 Patent Create a Substantial New Question of Patentability Based on Obviousness-Type Double Patenting

Claims 1-18 of the ’992 Patent are unpatentable over claims 1-5 of the ’261 Patent for obviousness-type double patenting. Claim 5 of the ’261 Patent (including the claims from which it depends) recites a specific formulation that falls within the scope of every claim of the ’992 Patent, and the Common Specification demonstrates that this formulation achieves the exact result that the Patent Owner used to overcome the examiner’s double patenting rejection. In addition to the discussion below, a detailed explanation of how the ’261 patent renders the claims of the ’992 patent unpatentable for obviousness-type double patenting is presented in the claim chart attached hereto as Appendix B.

1. Independent Claims 1 and 10 are Unpatentable For Double Patenting Over the ’261 Patent

As explained in Section II.C., during prosecution, Patent Owner did not dispute that the claims of the ’261 Patent contained each of the components of the claimed vial and formulation, *i.e.*, the claimed VEGF antagonist, an organic co-solvent, a buffer, and a stabilizing agent.

Rather, in response to the Examiner's obviousness-type double patenting rejection, Patent Owner amended the claims to recite the stability test results from the specification's examples and argued that those test results were not in the '261 Patent's claims. The phrase "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," only states an intended result and is therefore non-limiting. *See, e.g., In re: Copaxone Consol. Cases*, 906 F.3d at 1023. Even if this phrase is given patentable weight, this phrase does not render the claims of the '992 Patent patentably distinct from the claims of the '261 Patent for the reasons discussed below.

a. The '261 Patent Claims a Species Within the Scope of the '992 Patent Claims

As shown in the following table, the independent claims of the '992 Patent are not patentably distinct from claims 1-5 of the '261 Patent:

'992 Patent Independent Claims (claims 1 and 10)	'261 Patent Claim 5, which depends from claims 4, 3, 2, and 1
A formulation [or vial] comprising: a vascular endothelial growth factor (VEGF) antagonist,	"An ophthalmic formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising..." It was known to store protein formulations in a vial. <i>See, e.g., Exemplary Vial Pubs</i> (Ex. 9, 47:14-18; Ex. 10, 25:20-27).
an organic co-solvent,	'261 Patent, claim 3: "0.03% polysorbate"
a buffer,	'261 Patent, claim 3: "10 mM sodium phosphate buffer"
a stabilizing agent,	'261 Patent, claim 3: "5% sucrose"

wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and	'261 Patent, claim 1: “a) 1-100 mg/ml of a VEGF antagonist comprising the amino acid sequence of SEQ ID NO:4; ” Papadopoulos (Ex. 7) at 26:14-17 discloses that Regeneron’s VEGF antagonists, including VEGFR1R2-FcΔC1(a) (aflibercept, SEQ ID NO:4), were produced in CHO cells.
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.	'261 Patent, claim 5: “...VEGF antagonist at a concentration selected from the group consisting of 10 mg/ml, 20 mg/ml, 40 mg/ml , and 80 mg/ml.” Examples 3 and 4 of the '992 Patent evidence that the composition of claim 5, comprising 40 mg/mL of the VEGF antagonist, inherently has at least 98% of the VEGF antagonist present in native conformation following storage at 5°C for two months as measured by SEC.

As shown in the chart above, claim 5 of the '261 patent recites a specific formulation that falls within the broader genus claim of the '992 patent. As noted in Section II.A., the '992 Patent specification states that polysorbate is an “organic co-solvent,” sodium phosphate buffer is an exemplary “buffer,” and sucrose is a “stabilizing agent.” '992 Patent, 2:25-38. Likewise, the '992 Patent specification states that the VEGF antagonist of SEQ ID NO: 4 (as claimed in the '261 patent) is a preferred species of the genus of VEGF antagonist “fusion protein[s] comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component” (as claimed in the '992 Patent). '992 Patent, col. 2, lines 14-18; claim 4.

The formulation claimed in claim 5 the '261 Patent is a species of the broad formulation claimed in the '992 Patent, and thus anticipates, or at a minimum renders obvious, claims 1 and 10 of the '992 Patent. *See Perricone*, 432 F.3d at 1374; Section VI.D.1.a. *supra*. Moreover, as demonstrated below, the formulation recited in claim 5 of the '261 Patent achieves the same stability result claimed in the '992 Patent.

b. The Formulation Claimed in the '261 Patent Inherently Displays the Stability Recited in the '992 Patent's "Wherein" Clause

The fact that the '992 Patent recites a result obtained by the formulation—"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"—does not render its claims patentably distinct from those of the earlier-expiring '261 Patent. This result is an inherent characteristic of the formulation claimed in claim 5 of the '261 Patent, as demonstrated by the Common Specification.

As shown in the following table, claim 5 of the '261 Patent specifically recites the formulation tested in Examples 3 and 4 of the Common Specification:

Examples 3 & 4 of the Common Specification	'261 Patent, claim 5
40 mg/ml VEGF Trap (SEQ ID NO: 4)	10 mg/mL, 20 mg/mL, 40 mg/mL , or 80 mg/mL VEGF Trap comprising amino acids 27-457 of SEQ ID NO: 4
10 mM phosphate	10 mM sodium phosphate
40 mM NaCl	40 mM NaCl
0.03% polysorbate 20	0.03% polysorbate
5% sucrose	5% sucrose
pH 6.3	pH 6.2- 6.3

Although the claims of the '261 Patent do not expressly require that the polysorbate is polysorbate 20, the '261 Patent defines “polysorbate” as including two options: polysorbate 20 and polysorbate 80.⁴ '261 Patent at 2:10-12. Further, a POSA would understand that polysorbate 20 is the preferred polysorbate of the '261 Patent claims. Polysorbate 20 is used in every working example that includes a polysorbate. *See* '261 Patent at 7:67, 8:63, 9:23, 9:52, 10:26, 10:59, 11:20. A POSA would at once envisage polysorbate 20 when reading the '261 Patent's claim to “0.03% polysorbate,” so the claim anticipates this species. *See Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)) (holding a reference disclosure can anticipate a claim “if a person of skill in the art, reading the reference, would ‘at once envisage’ the claimed arrangement or combination.”); *AbbVie Inc.*, 764 F.3d at 1379 (same, in obviousness-type double patenting context).

As explained in Section VI.D.1.b. above, Examples 3 and 4 demonstrate that the above formulation has 99.2% and 99.1% of the VEGF trap in native conformation at two months, when the formulation is stored in vials or a prefilled syringe, respectively. *See* '992 Patent at Tables 3 and 4. Therefore, the formulations recited in the claims of the '261 Patent inherently have “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.”

⁴ It is appropriate to refer to portions of the reference patent's specification relating to the claimed invention and to use its teachings to define terms recited in the claims. MPEP § 804(II)(B); *In re Vogel*, 422 F.2d at 441-42; *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299 (Fed. Cir. 1999).

As explained in Section VI.D.1.b. above, the '992 Patent claims are not rendered patentably distinct from the claims of the '261 Patent by reciting the inherent result or property of the formulations claimed in the '261 Patent. *See, e.g., In re Crish*, 393 F.3d at 1258.

c. The Claims are Not Made Patentably Distinct by Reciting that the VEGF Antagonist is “Produced in” CHO Cells

As discussed in Section VI.D.1.c., the phrase “wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell” is a product-by-process limitation that does not distinguish the '992 Patent claims from those of the OTDP Reference Patents. Like the '594 Patent discussed above, the '261 Patent claims the same fusion protein of SEQ ID NO: 4 and teaches that it can be expressed in CHO cells. '261 Patent, claim 1, 6:2-5.

Moreover, it was entirely obvious to produce the VEGF fusion protein recited in the claims of the '261 Patent in CHO cells in view of Papadopoulos. *See, e.g.* Ex. 7, 12:19-26, 67:25–68:5.

Requester incorporates the explanations provided above in Section VI.D.1.c., which apply equally to the '261 Patent claims because both claim sets recite the same VEGF antagonist fusion protein of SEQ ID NO:4. The product in the product-by-process limitation of the '992 Patent is the same as or obvious over the VEGF antagonist protein claimed in the '261 Patent both because (1) the '261 Patent teaches that the claimed VEGF antagonist protein was produced in CHO cells, and (2) it was known from Papadopoulos that the same VEGF antagonist protein was produced in CHO cells.

d. The Claims are Not Made Patentably Distinct by Reciting a “Vial”

It would have been obvious for a POSA to place the formulation claimed in the '261 Patent in a vial for the same reasons discussed in Section VI.D.1.d. above with respect to the '594 Patent. Requester incorporates the explanations provided above in Section VI.D.1.d.

e. Claims 1 and 10 as a Whole are Unpatentable

In sum, claims 1-5 of the '261 Patent recite specific formulations that fall within the genus of formulations claimed in claims 1 and 10 of the '992 Patent, and therefore anticipate the '992 Patent claims. Neither the recitation of production of the protein in CHO cells, nor that the formulation is in a vial, lends patentability to the claims. Critically, the '992 Patent itself demonstrates that the formulation claimed in claims 1-5 of the '261 Patent inherently achieves the stability limitation recited in the '992 Patent's "wherein" clause. The technological teachings discussed above were not previously considered and discussed on the record during the prosecution of the application that resulted in the '992 Patent. This request presents the reference '261 Patent in a "new light" and in a different way that escaped review during earlier examination, and therefore presents a substantial new question of patentability.

Because the inserted test result element was also inherently part of the formulations claimed in the '261 Patent as evidenced by Examples 3-4 of the Common Specification, the Examiner erred by not maintaining the obviousness-type double patenting rejection. The claims of the '992 Patent were not rendered patentably distinct from the claims of the '261 Patent by Patent Owner's insertion of an intended result. The '992 Patent's formulation "cannot become nonobvious simply by ... claiming the [result].... To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Santarus, Inc.*, 694 F.3d at 1354. Thus, because independent claims 1 and 10 are anticipated by or obvious variants of claims 1-5 of the '261 Patent, claims 1 and 10 are unpatentable for obviousness-type double patenting.

2. Dependent Claims 2 and 11 are Unpatentable For Double Patenting Over the '261 Patent

Dependent claim 2 of the '992 Patent recites:

The vial of claim 1, wherein about 99% or more of the weight of the fusion protein is in native conformation.

Claim 11 is identical to claim 2 except the word “vial” in the preamble is substituted with the word “formulation” and it depends on independent claim 10. Requester incorporates the explanations provided above for claims 1 and 10 in Section VI.E.1. above.

The same examples from Common Specification discussed above also evidence that the claimed formulations had test results showing that “99% or more of the weight of the fusion protein is in native conformation following storage at 5°C. for two months” as recited in claims 2 and 11. To the extent that this intended result is given patentable weight, it is inherently achieved by the formulations claimed in the '261 Patent as evidenced by Examples 3-4 of the Common Specification. Therefore, the Examiner erred by not maintaining the obviousness-type double patenting rejection. The claims of the '992 Patent were not rendered patentably distinct from the claims of the '261 Patent by Patent Owner's insertion of an intended result. Thus, because claims 2 and 11 are anticipated by or obvious variants of claims 1-5 of the '261 Patent, claims 2 and 11 are unpatentable for obviousness-type double patenting.

3. Dependent Claims 3, 4, 12 and 13 are Unpatentable For Double Patenting Over the '261 Patent

As explained in Section VI.D.3. above, claims 3, 4, 12, and 13 of the '992 Patent all encompass a protein that “comprises amino acids 27-457 of SEQ ID NO: 4.” Requester also incorporates the explanations provided for claims 1 and 10 in Section VI.E.1. above.

Claim 1 of the '261 Patent recites “a VEGF antagonist comprising the amino acid sequence of SEQ ID NO:4,” which is a species of the “protein compris[ing] amino acids 27-457 of SEQ ID NO:4” recited in claims 4 and 13 of the '992 Patent, and also necessarily falls within the broader genus of claims 3 and 12 of the '992 Patent (from which claims 4 and 13 depend).

Therefore, the Examiner erred by not maintaining the obviousness-type double patenting rejection. Thus, because claims 3, 4, 12 and 13 are anticipated by or obvious variants of claims 1-5 of the '261 Patent, these claims are unpatentable for obviousness-type double patenting.

4. Dependent Claims 5 and 14 are Unpatentable For Double Patenting Over the '261 Patent

Dependent claim 5 of the '992 Patent recites:

The vial of claim 4, wherein the VEGF antagonist is a dimer of the fusion protein.

Claim 14 is identical to claim 5 except the word “vial” in the preamble is substituted with the word “formulation” and it depends on independent claim 10. Requester incorporates the explanations provided above for claims 1 and 10 in Section VI.E.1. above.

As explained in Section VI.D.4. above, the recitation that the VEGF antagonists is a dimer is not a patentable distinction, as this is merely a property of the VEGF antagonist of SEQ ID NO:4 claimed in the '261 Patent and known in the prior art. *See* Ex. 8 ¶¶ [0086], [0197] (confirming aflibercept, SEQ ID NO: 4, is a dimer); Ex. 7, 70:23-24 (confirming the closely related VEGF trap “Flt1D2.Flk1D3.FcC1(a)” of SEQ ID NO:2 is a “dimer”), 12:10, 25:23-35 (noting intermolecular disulfide bonds in the Fc region); Fig 24B-C (identifying the Fc region in the aflibercept sequence).

Therefore, the Examiner erred by not maintaining the obviousness-type double patenting rejection. The claims of the '992 Patent were not rendered patentably distinct from the claims of the '261 Patent by Patent Owner's insertion of an intended result. Thus, because claims 5 and 14 are anticipated by or obvious variants of claims 1-5 of the '261 Patent, these claims are unpatentable for obviousness-type double patenting.

5. Dependent Claims 6-9 and 15-18 are Unpatentable For Double Patenting Over the '261 Patent

As detailed in Section VI.D.5. above, dependent claims 6-9 and 15-18 encompass a formulation comprising polysorbate 20, sucrose, and/or phosphate buffer, in various combinations. Requester also incorporates the explanations provided above for claims 1 and 10 in Section VI.E.1. above.

Claims 3-5 of the '261 Patent recite, in a single formulation, the same elements as claims 6-9 and 15-18 of the '992 Patent, *i.e.*, “10 mM sodium **phosphate buffer**, 40 mM NaCl, 0.03% **polysorbate**, and 5% **sucrose**.” As explained in Section VI.E.1.b. above, a POSA would at once envisage polysorbate 20 when reading the '261 Patent's claim to “0.03% polysorbate,” so this species is not patentably distinct from the earlier-claimed “polysorbate.” *See* '261 Patent at 2:10-12, 7:67, 8:63, 9:23, 9:52, 10:26, 10:59, 11:20; *AbbVie, Inc.*, 764 F.3d at 1379. This is the same formulation that inherently achieves the results recited in the “wherein” clauses of claims 1, 2, 10 and 11 of the '992 Patent. *See* Sections VI.E.1.b. and VI.E.2. *supra*. Claims 6-9 and 15-18 of the '992 Patent thus are not patentably distinct over the '261 Patent claims.

Therefore, the Examiner erred by not maintaining the obviousness-type double patenting rejection. The claims of the '992 Patent were not rendered patentably distinct from the claims of the '261 Patent by Patent Owner's insertion of an intended result. Thus, because claims 6-9 and 15-18 are anticipated by or obvious variants of claims 1-5 of the '261 Patent, claims 6-9 and 15-18 are unpatentable for obviousness-type double patenting.

F. SNQ3: The Claims of the '489 Patent Create a Substantial New Question of Patentability Based on Obviousness-Type Double Patenting

Claims 1-18 of the '992 Patent are unpatentable over claims 1-29 of the '489 Patent for obviousness-type double patenting. The independent claims of the '489 Patent are very similar to the independent claims the '992 Patent. Independent claims 1 and 26 of the '489 Patent claim

a formulation and a vial, respectively, comprising a VEGF antagonist protein (defined by the same genus as the independent claims of the '992 Patent); an organic co-solvent; a buffer; and a stabilizer or tonicity agent. Dependent claim 24 recites that the protein is expressed in a CHO cell. The '489 Patent's independent claims are more specific than those of the '992 Patent in that they recite a concentration range for the formulation components.

Dependent claims 5, 7, 9, 15, 18, 21, and 25 of the '489 Patent (and the claims from which they depend) direct the POSA to each of the specific formulation components described in Examples 3 and 4 of the Common Specification (*e.g.*, 0.03% polysorbate 20 as the organic co-solvent, phosphate buffer, 5% sucrose as the stabilizing agent, the VEGF antagonist protein of SEQ ID NO:4, and pH 6.2-6.3). The Common Specification demonstrates that the formulation taught by these claims as a whole achieves the exact result that the Patent Owner used to overcome the examiner's double patenting rejection.

In addition to the discussion below, a detailed explanation of how the '489 patent renders the claims of the '992 patent unpatentable for obviousness-type double patenting is presented in the claim chart attached hereto as Appendix C.

The '489 Patent was not cited by the examiner during prosecution of the '992 Patent. The proposed rejection "presents a new, non-cumulative technological teaching that was not previously considered and discussed on the record during the prosecution of the application that resulted in the patent for which reexamination is requested," at least because the Examiner did not recognize that the Examples in the Common Specification demonstrate that the earlier-claimed formulations achieve the stability result recited in the '992 Patent's "wherein" clause. MPEP § 2216. Additionally, like the '992 Patent, the '489 Patent recites a set of claims to a "formulation" and a set of claims to a "vial" containing the formulation, which evidences that

there is no basis to conclude that placing a formulation in a vial is patentably distinct from a formulation in general or a formulation in a syringe, as discussed above for the other OTDP Reference Patents. As demonstrated below, the claims of the '489 Patent create a substantial new question of patentability.

1. Independent Claims 1, 2, 10 and 11 are Unpatentable For Double Patenting Over the '489 Patent Claims

The Examiner erroneously did not reject the claims of the '992 Patent for double patenting over the claims of the '489 Patent. As shown in the following table, the independent claims of the '992 Patent are not patentably distinct from claims 1-29 of the '489 Patent:

'992 Patent Independent Claims (Claims 1 and 10)	'489 Patent, Claims 1, 5, 7, 9, 15, 18, 21, 24, 25 and 26
A vial [or formulation] comprising: a vascular endothelial growth factor (VEGF) antagonist,	'489 Patent, claim 1: "A formulation comprising: (a) 1-100 mg/mL of a VEGF-specific fusion protein antagonist;" '489 Patent, claim 26: "A vial containing a formulation comprising: (a) 1-100 mg/mL of a VEGF-specific fusion protein antagonist."
an organic co-solvent,	'489 Patent, claim 1: "(c) 0.01-5% of an organic co-solvent"
a buffer, and	'489 Patent, claim 1: "(b) 5-40 mM of a buffer"
a stabilizing agent,	'489 Patent, claim 1: "(d) a stabilizer or 30-150 mM of a tonicity agent"

wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and	'489 Patent, claim 1: "... wherein ... the VEGF-specific fusion protein antagonist comprises an Ig domain 2 of human VEGF receptor 1, an Ig domain 3 of human VEGF receptor 2, and a multimerizing component." '489 Patent, claim 24: "The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist is expressed in a Chinese hamster ovary (CHO) cell."
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.	'489 Patent, claims 1 and 26: "...wherein at least 90% of the total weight of the VEGF-specific fusion protein antagonist is not present as an aggregate..." Example 3 of the '992 Patent evidences the inherent stability results for a formulation taught by the combination of claims 1, 5, 7, 9, 15, 18, 21, and 25. <i>See Table infra.</i>

As is apparent from the above claim chart, claims 1 and 26 of the '489 Patent are directed to a formulation and vial, respectively, having the same components recited in the '992 Patent's independent claims. The '489 Patent claims also specify the concentrations of the formulation components. The earlier-expiring '489 Patent claims are a species that falls within the genus of claims 1 and 10 of the '992 Patent, and thus claims 1 and 10 of the '992 Patent are invalid for obviousness-type double patenting. *See Perricone*, 432 F.3d at 1374.

The '992 Patent's recitation of an intended result in the "wherein" clause is not limiting and therefore does not render the claims patentably distinct. *In re Copaxone Consol. Cases*, 906 F.3d at 1023. Even if this phrase is given patentable weight, it does not render the claims of the '992 Patent patentably distinct from the claims of the '489 Patent. As an initial matter, the independent claims of the '489 Patent recite the result that "at least 90% of the total weight of the VEGF-specific fusion protein antagonist is not present as an aggregate," which is achieved by

the same working examples in the specification that achieve the result now claimed in the '992 Patent. '489 Patent, 7:45-12:18 (Examples 1-8); *see AbbVie Inc.*, 764 F.3d at 1380-81 (holding that in an obviousness-type double patenting inquiry, the specification may be consulted to determine “whether the claims merely define an obvious variation of what is earlier disclosed and claimed”).

Moreover, and as an independent basis for finding the claims not patentably distinct, the Common Specification demonstrates that formulations taught by the claims of the '489 Patent as a whole inherently achieve the level of stability recited in claims 1, 2, 10, and 11 of the '992 Patent. The dependent claims of the '489 Patent recite all of the specific formulation ingredients of Examples 3 and 4 of the Common Specification, and teach, or at least render obvious, their use in combination, as shown in the following table:

Examples 3 & 4 of the Common Specification	'489 Patent, Claims 5, 7, 9, 15, 18, 21, 25
40 mg/ml VEGF Trap (SEQ ID NO:4)	“the VEGF-specific fusion protein antagonist is present at a concentration of about 10, about 20, about 30, about 40 , about 50, about 60, about 70, or about 80 mg/ml ” (claim 5); “the VEGF-specific fusion protein antagonist comprises glycosylated Asn residues corresponding to Asn residues at positions 62, 94, 129, 222, and 308 of SEQ ID NO: 4 ” (claim 25)
10 mM phosphate	“the buffer comprises sodium phosphate present at a concentration of 10 mM ” (claim 7)
40 mM NaCl	“ sodium chloride is present at a concentration of 20 mM, 40 mM , 50 mM, 100 mM, or 135 mM” (claim 18)
0.03% polysorbate 20	“the organic co-solvent is polysorbate 80 or polysorbate 20 present at a concentration of 0.015%, 0.03% or 0.1%” (claim 15)
5% sucrose	“ sucrose is present at a concentration of 5% ” (claim 21)

pH 6.3	“the pH is about pH 6.2-6.3 ” (claim 9)
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Although the dependency structure of the claims of the '489 patent is such that the claims do not recite each of the specific components of Examples 3 and 4 together in a single formulation, a POSA reading the claims as a whole would have at once envisaged—or at least found it obvious to prepare—a formulation comprising each of the most specific claimed elements. The independent claims of the '489 patent (claims 1 and 26) each require a formulation comprising (a) a VEGF-specific fusion protein antagonist; (b) a buffer; (c) an organic co-solvent; and (d) a stabilizer or tonicity agent. The dependent claims listed in the table above are the most specific recitations of each of these components found in the '489 Patent claims. Indeed, the dependent claims of the '489 Patent direct the POSA to a small genus of formulations (*i.e.*, 8 possible concentrations of VEGF antagonist; 5 possible concentrations of sodium chloride; 8 possible concentrations/types of organic co-solvent (across claims 13 and 15); and a very narrow pH range). The dependent claims as a whole direct the POSA to the exact formulations exemplified in Examples 3 and 4 of the Common Specification, rendering those formulations anticipated by or at least obvious over the '489 Patent claims as a whole. *See Kennametal*, 780 F.3d at 1381-83 (holding claims anticipated by a reference that taught to combine types of components, and provided multiple options for each type of component resulting in about 10,000 possible combinations).

As explained in Section VI.D.1.b. above, Examples 3 and 4 demonstrate that the formulation in the above chart has 99.2% and 99.1% of the VEGF trap in native conformation at two months, when the formulation is stored in vials or a prefilled syringe, respectively. *See* '992 Patent at Tables 3 and 4. Therefore, the claims of the '489 Patent direct the POSA to formulations having 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” as recited in claims 1 and 10 of the ’992 Patent. For the same reason, these formulations also meet the limitation of claims 2 and 11 of the ’992 patent, which recite “wherein about 99% or more of the weight of the fusion protein is in native conformation.”

The ’992 Patent claims are not rendered patentably distinct from the claims of the ’489 Patent by reciting a property of formulations that are anticipated or rendered obvious by the claims of the earlier expiring ’489 Patent. *See, e.g., Crish*, 393 F.3d at 1258. Even if the ’489 Patent claims only render the formulation of Examples 3 and 4 obvious, “an obvious formulation cannot become nonobvious simply by ... claiming the result[.]” *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d at 1354; *see also Alcon Research*, 687 F.3d at 1369 (holding that a property “necessarily present” in an obvious formulation does not patentably distinguish the claims). Thus, because claims 1, 2, 10, and 11 of the ’992 Patent are anticipated by, or obvious variants of, the claims of the ’489 Patent, these claims are unpatentable for obviousness-type double patenting.

A very strong case for obviousness-type double patenting based on anticipation and obviousness over the ’489 Patent claims exists as set out above. In addition, as a separate and independent reason for finding obviousness-type double patenting, the situation here is very similar to *In re Schneller*, 397 F.2d 350 (CCPA 1968). In *Schneller*, the patent owner disclosed an invention comprising elements ABCXY and obtained earlier-expiring claims to “BCX and ABCX, but so claiming these combinations as to cover them no matter what other feature is incorporated in them, thus covering effectively ABCXY.” 397 F.2d at 355-56. The court held that the patent owner was not entitled “many years later” to obtain “claims directed to ABCY and ABCXY,” because the “protection he already had would be extended, albeit is [sic]

somewhat different form, for several years beyond the expiration of his [first] patent.” *Id.* at 356; *see also In re Metoprolol Succinate Patent Litig.*, 494 F.3d 1011, 1018 (Fed. Cir. 2007) (noting *Schneller* controls over earlier CCPA cases discussing double patenting).

Here, the ’489 Patent claims formulations comprising VEGF-specific fusion protein antagonists, with separate dependent claims 5, 9, 15, 18, 21, and 25 reciting a formulation “comprising” more specific components (*e.g.*, claims to AB, AC, AD, AE, and AF), all of which *cover* the formulation in Examples 3 and 4 (*e.g.*, the specific formulation ABCDEF), which is disclosed in the Common Specification to achieve the results now claimed in the “wherein” clauses of the ’992 Patent. Allowing the claims of the ’992 Patent to expire six years later than the claims of the ’489 Patent would unjustly extend the effective term of the ’489 Patent. A nonstatutory double patenting rejection is thus also applicable here based on equitable principles. *See* MPEP § 804(II)(B)(3) (noting that “the fundamental reason for nonstatutory double patenting – to prevent unjustified timewise extension of patent rights – is itself enforceable no matter how the extension is brought about”). Thus, because claims 1, 2, 10, and 11 of the ’992 Patent constitute an unjustified or improper timewise extension of the right to exclude granted by the ’489 Patent, claims 1, 2, 10 and 11 of the ’992 Patent are unpatentable for obviousness-type double patenting.

2. Dependent Claims 3, 4, 12 and 13 are Unpatentable For Double Patenting Over the ’489 Patent

As explained in Section II.A. above, claims 3, 4, 12, and 13 of the ’992 Patent all encompass a protein that “comprises amino acids 27-457 of SEQ ID NO: 4.” Requester incorporates the explanations provided above for claims 1 and 10 in Section VI.F.1. above.

Claim 25 of the ’489 Patent recites: “The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist comprises glycosylated Asn residues corresponding to Asn

residues at positions 62, 94, 149, 222, and 308 of SEQ ID NO:4.” Claim 25 encompasses and teaches, or at least strongly suggests, the use of the fusion protein of SEQ ID NO: 4 (*e.g.*, the fusion protein comprising amino acids 27-457 of SEQ ID NO: 4), which is the subject matter claimed in claims 4 and 13 of the '992 Patent, and encompassed by claims 3 and 12 of the '992 Patent.

Therefore, because claims 3, 4, 12 and 13 are anticipated by, or obvious variants of, the claims of the '489 Patent, and based on the equitable reason of preventing unjustified or improper timewise extension of the “right to exclude,” claims 3, 4, 12, and 13 are unpatentable for obviousness-type double patenting.

3. Dependent Claims 5-9 and 14-18 are Unpatentable For Double Patenting Over the '489 Patent

As shown in Appendix C, the elements of each of the remaining dependent claims of the '992 Patent (claims 5-9 and 14-18) are also rendered obvious by the claims of the '489 Patent. Claims 5 and 14 recite that the VEGF antagonist is a dimer, which is recited in claim 23 of the '489 patent. Claims 6-9 and 15-18 of the '992 Patent recite the use of certain components of the formulations described in Examples 3 and 4 of the Common Specification, which are anticipated or rendered obvious by the claims of the '489 Patent as discussed in Section VI.F.1. above. For these reasons, and based on the equitable reason of preventing unjustified or improper timewise extension of the “right to exclude,” dependent claims 5-9 and 14-18 are unpatentable for obviousness-type double patenting.

VII. NOTIFICATION OF PATENTEE

The signature below indicates that a true and correct copy of this request and all accompanying papers have been served in accordance with 37 C.F.R. § 1.510 on the Patent Owner at the correspondence address in the patent file, as provided for in 37 C.F.R. § 1.33(c):

REGENERON - BOZICEVIC, FIELD & FRANCIS LLP

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VIII. CONCLUSION

As discussed above, Requestor has explained how each of the OTDP Reference Patents, either alone or in combination with Papadopoulos and/or the Exemplary Vial Pubs., presents a new, non-cumulative technological teaching that a reasonable examiner would consider to be important in determining whether or not claims 1-18 of the '992 Patent are patentable, and thus raises a substantial new question of patentability. As set forth above and in the claim charts in Appendices A through C, the OTDP Reference Patents cited herein render claims 1-18 unpatentable for nonstatutory obviousness-type double patenting. Accordingly, it is respectfully requested that the Office grant this Request for *ex parte* Reexamination of the '992 Patent, and, after further examination in view of the OTDP Reference Patents and the preceding discussion, reject and cancel claims 1-18 of the '992 Patent.

As noted above, Requester certifies that a true and correct copy of this Request for *ex parte* Reexamination, together with the references relied upon, was served on the patent owner.

Dated: February 11, 2020

Respectfully submitted,

By /Christopher J. Maier/
Christopher J. Maier
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APPENDIX A – '594 PATENT CLAIM CHART

'992 Patent	'594 Patent, Claim 5, which depends from claims 4, 3, 2, and 1.
Claim 1	
A vial [or formulation] comprising: a vascular endothelial growth factor (VEGF) antagonist,	'594 Patent, claim 1: “A pre-filled syringe suitable for intravitreal administration comprising a 1 mL luer glass syringe fitted with a plunger and a stable ophthalmic formulation of a vascular endothelial growth factor (VEGF) trap...” It was known to store VEGF antagonist protein formulations in a vial. <i>See, e.g.</i>, Exemplary Vial Pubs. (Ex. 9, 47:14-18; Ex. 10, 25:20-27).
an organic co-solvent	'594 Patent, claim 5: “The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF trap, 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, at pH 6.2-6.4.”
a buffer	'594 Patent, claim 5: “The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF trap, 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, at pH 6.2-6.4.”
a stabilizing agent	'594 Patent, claim 5: “The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF trap, 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, at pH 6.2-6.4.”
wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary	'594 Patent, claim 1: “... a vascular endothelial growth factor (VEGF) trap, which consists of (i) a receptor component consisting essentially of an

(CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and	immunoglobulin-like domain 2 of a first VEGF receptor and an immunoglobulin-like domain 3 of a second VEGF receptor, and (ii) a multimerizing component” ’594 Patent, claim 4: “wherein the VEGF trap consists of amino acids 27-457 of SEQ ID NO:4.” Papadopoulos (Ex. 7, 26:14-17) discloses that Regeneron’s VEGF trap molecules, including VEGFR1R2-FcΔC1(a) (aflibercept), SEQ ID NO:4, were produced in CHO cells.
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.	’594 Patent, claim 3: “The pre-filled syringe according to claim 2, wherein the VEGF trap is stable for at least 4 months.” To the extent that this intended result is given patentable weight, Examples 3 and 4 of the Common Specification evidence the inherent stability results for the formulation of claim 5 of the ’594 Patent. <i>See, e.g.</i>, ’992 Patent, 8:62-67, Table 3 (Example 3: “A liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5°C... in 3 ml glass vials and samples tested at 0.5, 1, 2, 3, and 4 months” and showed that the formulation has 99.2% of the VEGF trap in native conformation at two months), ’992 Patent, 9:1-9:54, Table 4 (Example 4: “A liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 40 mM. NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5°C. in 1 ml prefilled luerglass syringe with 4023/50 FLUROTEC™ coated (elastomer coated) plunger and samples tested at 0.5. 1, 2, 3, and 4 months” and showed that the formulation has 99.1% of the VEGF trap in native conformation at two months).

Claims 2 and 11	
The vial [or formulation] of claim 1, wherein about 99% or more of the weight of the fusion protein is in native conformation.	See claim 1
Claims 3 and 12	
The vial [or formulation] of claim 1, 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.	See claim 1 '594 Patent, claim 2: "The pre-filled syringe of claim 1, wherein the first VEGF receptor is Flt1, and the second VEGF receptor is Flk1 or Flt4."
Claims 4 and 13	
The vial [or formulation] of claim 3, wherein the fusion protein comprises amino acids 27-457 of SEQ ID NO:4.	See claim 1 '594 Patent, claim 4: "The pre-filled syringe according to claim 3, wherein the VEGF trap consists of amino acids 27-457 of SEQ ID NO:4."
Claims 5 and 14	
The vial [or formulation] of claim 4, wherein the VEGF antagonist is a dimer of the fusion protein.	See Claims 4 and 13 above. The '594 Patent admits that the protein of SEQ ID NO: 4 forms dimers.'594 Patent, 6:7-8 ("Preferably, the VEGF antagonist is a dimer composed of two fusion proteins of SEQ ID NO:4.") Papadopolous discloses that the VEGF trap molecules form dimers. (Ex. 7, 12:10, 70:23-24) A POSA also would understand that the VEGF trap consisting of amino acids 27-457 of SEQ ID NO:4 contains the Fc region of a human IgG molecule, and therefore forms dimers.

Claims 6 and 15	
The vial [or formulation] of claim 5, wherein the organic co-solvent is selected for the group consisting of polysorbate 20, polysorbate 90, polyethylene glycol (PEG), PEG3350, and propylene glycol.	'594 Patent, claim 5: “The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF trap, 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20 , 5% sucrose, at pH 6.2-6.4.”
Claims 7 and 16	
The vial [or formulation] of claim 6, wherein the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.	'594 Patent, claim 5: “The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF trap, 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose , at pH 6.2-6.4.”
Claims 8 and 17	
The vial [or formulation] of claim 1, wherein the organic co-solvent is polysorbate 20 and the stabilizing agent is sucrose.	See claim 1 '594 Patent, claim 5: “The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF trap, 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20 , 5% sucrose , at pH 6.2-6.4.”
Claims 9 and 18	
The vial [or formulation] of claim 1, wherein the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose.	See claim 1 '594 Patent, claim 5: “The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF trap, 10 mM phosphate , 40 mM NaCl, 0.03% polysorbate 20 , 5% sucrose , at pH 6.2-6.4.”

APPENDIX B – '261 PATENT CLAIM CHART

'992 Patent	'261 Patent, Claim 5, which depends from claims 4, 3, 2, and 1.
Claim 1	
A vial [or formulation] comprising: a vascular endothelial growth factor (VEGF) antagonist,	'261 Patent, claim 1: “An ophthalmic formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising...” It was known to store VEGF antagonist protein formulations in a vial. <i>See, e.g.</i> , Exemplary Vial Pubs. (Ex. 9, 47:14-18; Ex. 10, 25:20-27.)
an organic co-solvent	'261 Patent, claim 3: “The ophthalmic formulation of claim 2, comprising about 1-100 mg/ml of the VEGF antagonist, 10mM sodium phosphate buffer, 40mM NaCL, 0.03% polysorbate , and 5% sucrose, pH about 6.2-6.3.”
a buffer	'261 Patent, claim 3: “The ophthalmic formulation of claim 2, comprising about 1-100 mg/ml of the VEGF antagonist, 10mM sodium phosphate buffer , 40mM NaCL, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3.”
a stabilizing agent	'261 Patent, claim 3: “The ophthalmic formulation of claim 2, comprising about 1-100 mg/ml of the VEGF antagonist, 10mM sodium phosphate buffer, 40mM NaCL, 0.03% polysorbate, and 5% sucrose , pH about 6.2-6.3.”
wherein the VEGF antagonist is a fusion protein produced in a	'261 Patent, claim 1:

Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and	a) 1-100 mg/ml of a VEGF antagonist comprising the amino acid sequence of SEQ ID NO:4; Papadopoulos (Ex. 7, 26:14-17) discloses that VEGF antagonists, including VEGFR1R2-FcΔC1(a) (aflibercept), SEQ ID NO: 4 , were produced in CHO cells .
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.	To the extent that this intended result is given patentable weight, Examples 3 and 4 of the Common Specification evidence the inherent stability results for the formulation of claim 5 of the '261 Patent, comprising 40 mg/ml of the VEGF antagonist. <i>See, e.g.</i> '992 Patent, 8:62-9:54, Tables 3-4. '261 Patent, claim 5: "The ophthalmic formulation of claim 4 [dependent from claim 3], comprising VEGF antagonist at a concentration selected from the group consisting of 10 mg/ml, 20 mg/ml, 40 mg/ml , and 80 mg/ml." Example 3: "A liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5°C. in 3 ml glass vials and samples tested at 0.5, 1, 2, 3, and 4 months" and showed that the formulation has 99.2% of the VEGF trap in native conformation at two months. '261 Patent, 8:60-67, Table 3; <i>see also</i> '261 Patent, 9:21-30 (Example 4), Table 4.
Claims 2 and 11	
The vial [or formulation] of claim 1, wherein about 99% or more of the weight of the fusion protein is in native conformation.	See claim 1 above.

Claims 3 and 12	
The vial [or formulation] of claim 1 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.	'261 Patent, claim 1: “a VEGF antagonist comprising ... the amino acid sequence of SEQ ID NO:4 ,” which is a species of the “protein compris[ing] amino acids 27-457 of SEQ ID NO:4 ”
Claims 4 and 13	
The vial [or formulation] of claim 3, wherein the fusion protein comprises amino acids 27-457 of SEQ ID NO:4.	'261 Patent, claim 1: “a VEGF antagonist comprising ... the amino acid sequence of SEQ ID NO:4 ,” which is a species of the “protein compris[ing] amino acids 27-457 of SEQ ID NO:4 ”
Claims 5 and 14	
The vial [or formulation] of claim 4, wherein the VEGF antagonist is a dimer of the fusion protein.	See claims 4 and 13 above. The '261 Patent admits that the protein of SEQ ID NO: 4 forms dimers. '261 Patent, 6:7-8 (“Preferably, the VEGF antagonist is a dimer composed of two fusion proteins of SEQ ID NO:4.”). Papadopolous discloses that the VEGF trap molecules form dimers. (Ex. 7, 12:10, 70:23-24). A POSA also would understand that the VEGF trap “consisting of amino acids 27-457 of SEQ ID NO:4 ” contains the Fc region of a human IgG molecule, and therefore forms dimers.
Claims 6 and 15	
The vial [or formulation] of claim 5, wherein the organic co-solvent is selected for the group consisting of polysorbate 20, polysorbate 90,	'261 Patent, claim 1: “b) 0.01-5% of one or more organic co-solvent(s) which is one or more of polysorbate, polyethylene glycol (PEG), and propylene glycol;”

polyethylene glycol (PEG), PEG3350, and propylene glycol.	'261 Patent, claim 3: “The ophthalmic formulation of claim 2, comprising about 1-100 mg/ml of the VEGF antagonist, 10mM sodium phosphate buffer, 40mM NaCl, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3.” The '261 specification defines polysorbate as including “for example, polysorbate 20 or polysorbate 80.” ‘261 pat. 2:10-12.
Claims 7 and 16	
The vial [or formulation] of claim 6, wherein the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.	'261 Patent, claim 3: “... 10 mM sodium phosphate buffer, 40 mM NaCl, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3.”
Claims 8 and 17	
The vial [or formulation] of claim 1, wherein the organic co-solvent is polysorbate 20 and the stabilizing agent is sucrose.	See claims 6 and 15 above. '261 Patent, claim 3: “... 10 mM sodium phosphate buffer, 40 mM NaCl, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3.”
Claims 9 and 18	
The vial [or formulation] of claim 1, wherein the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose.	See claims 6 and 15 above. '261 Patent, claim 3: “... 10 mM sodium phosphate buffer, 40 mM NaCl, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3.”

APPENDIX C – '489 PATENT CLAIM CHART

'992 Patent	'489 Patent, Claims 1, 4, 5, 7, 15, 18, and 24
Claim 1	
A vial [or formulation] comprising: a vascular endothelial growth factor (VEGF) antagonist,	'489 Patent, claim 1: “A formulation comprising: (a) 1-100 mg/mL of a VEGF-specific fusion protein antagonist.” '489 Patent, claim 26: “a vial containing a formulation comprising: (a) 1-100 mg/mL of a VEGF-specific fusion protein antagonist.”
an organic co-solvent	'489 Patent, claim 1: “(c) 0.01-5% of an organic co-solvent”
a buffer, and	'489 Patent, claim 1: “(b) 5-40 mM of a buffer;”
a stabilizing agent	'489 Patent, claim 1: “(d) a stabilizer or 30-150 mM of a tonicity agent”
wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component,	'489 Patent, claim 1: “wherein ... the VEGF-specific fusion protein antagonist comprises an Ig domain 2 of human VEGF receptor 1, an Ig domain 3 of human VEGF receptor 2, and a multimerizing component.” '489 Patent, claim 24: “The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist is expressed in a Chinese hamster ovary (CHO) cell.”
wherein at least 98% of the VEGF antagonist is present	To the extent that this intended result is given patentable weight, Examples 3-4 of the Common Specification evidence the inherent

in native conformation following storage at 5°C for two months as measured by size exclusion chromatography.	stability results for the formulation taught by the combination of claims 1, 5, 7, 9, 15, 18, and 21 (99.2% and 99.1% of the VEGF antagonist in native conformation at two months as measured by SEC). '489 Patent, claim 5: “The formulation of claim 4, where the VEGF-specific fusion protein antagonist is present at a concentration of about 10, about 20, about 30, about 40, about 50, about 60, about 70, or about 80 mg/ml.” '489 Patent, claim 7: “The formulation of claim 6, wherein the buffer comprises sodium phosphate present at a concentration of 10 mM.” '489 Patent, claim 9: “The formulation of claim 1, wherein the pH is about pH 6.2-6.3.” '489 Patent, claim 15: “The formulation of claim 14, wherein the organic co-solvent is polysorbate 80 or polysorbate 20 present at a concentration of 0.015%, 0.03% or 0.1%.” '489 Patent, claim 18: “The formulation of claim 17, wherein the sodium chloride is present at a concentration of 20 mM, 40 mM, 50 mM, 100 mM, or 135 mM.” '489 Patent, claim 21: “The formulation of claim 20, wherein the sucrose is present at a concentration of 5%.” '489 Patent, claim 25: “The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist comprises glycosylated Asn residues corresponding to Asn residues at positions 62, 94, 149, 222, and 308 of SEQ ID NO:4.”
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Claims 2 and 11	
The vial [or formulation] of claim 1, wherein about 99% or more of the weight of the fusion protein is in native conformation.	See claim 1
Claims 3 and 12	
The vial [or formulation] of claim 1, 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.	See claim 1 '489 Patent, claim 25: "The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist comprises glycosylated Asn residues corresponding to Asn residues at positions 62, 94, 149, 222, and 308 of SEQ ID NO:4 ."
Claims 4 and 13	
The vial [or formulation] of claim 3, wherein the fusion protein comprises amino acids 27-457 of SEQ ID NO:4.	See claims 1, 3 and 12. '489 Patent, claim 25: "The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist comprises glycosylated Asn residues corresponding to Asn residues at positions 62, 94, 149, 222, and 308 of SEQ ID NO:4 ."
Claims 5 and 14	
The vial [or formulation] of claim 4, wherein the VEGF antagonist is a dimer of the fusion protein.	'489 Patent, claim 23: "The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist is a dimer ."
Claims 6 and 15	
The vial [or formulation] of claim 5, wherein the organic co-solvent is	'489 Patent, claim 15:

selected for the group consisting of polysorbate 20 , polysorbate 90, polyethylene glycol (PEG), PEG3350, and propylene glycol.	“The formulation of claim 14, wherein the organic co-solvent is polysorbate 80 or polysorbate 20 present at a concentration of 0.015%, 0.03% or 0.1%.”
Claims 7 and 16	
The vial [or formulation] of claim 6, wherein the stabilizing agent is selected from the group consisting of sucrose , sorbitol, glycerol, trehalose, and mannitol.	See claim 1 '489 Patent, claim 20: “The formulation of claim 19, wherein the stabilizer comprises sucrose .”
Claims 8 and 17	
The vial [or formulation] of claim 1, wherein the organic co-solvent is polysorbate 20 and the stabilizing agent is sucrose.	See claim 1 '489 Patent, claim 15: “The formulation of claim 14, wherein the organic co-solvent is polysorbate 80 or polysorbate 20 present at a concentration of 0.015%, 0.03% or 0.1%.” '489 Patent, claim 20: “. . . the stabilizer comprises sucrose ”

Claims 9 and 18	
The vial [or formulation] of claim 1, wherein the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose.	See claim 1 '489 Patent, claim 15: “The formulation of claim 14, wherein the organic co-solvent is polysorbate 80 or polysorbate 20 present at a concentration of 0.015%, 0.03% or 0.1%.” '489 Patent, claim 6: “. . . the buffer comprises a phosphate buffer” '489 Patent, claim 7: “. . . the buffer comprises sodium phosphate present at a concentration of 10 mM” '489 Patent, claim 20: “. . . the stabilizer comprises sucrose”

APPENDIX D – ALIGNMENT OF SEQ ID NO: 4 OF '992 PATENT AND SEQ ID NO: 11 OF VITTI (EXHIBIT 8)

100.0% identity in 458 residues overlap; Score: 2437.0; Gap frequency: 0.0%

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SEQ4of992      1  MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTS
SEQ11          1  MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTS
                  *****

SEQ4of992     61  PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIIISNATYKEIGLLTCEATVNGHLYKTNLYT
SEQ11         61  PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIIISNATYKEIGLLTCEATVNGHLYKTNLYT
                  *****

SEQ4of992    121  HRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRD
SEQ11       121  HRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRD
                  *****

SEQ4of992    181  LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPC
SEQ11       181  LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPC
                  *****

SEQ4of992    241  PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
SEQ11       241  PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
                  *****

SEQ4of992    301  KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
SEQ11       301  KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
                  *****

SEQ4of992    361  TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFFLYSK
SEQ11       361  TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFFLYSK
                  *****

SEQ4of992    421  LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ11       421  LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
                  *****

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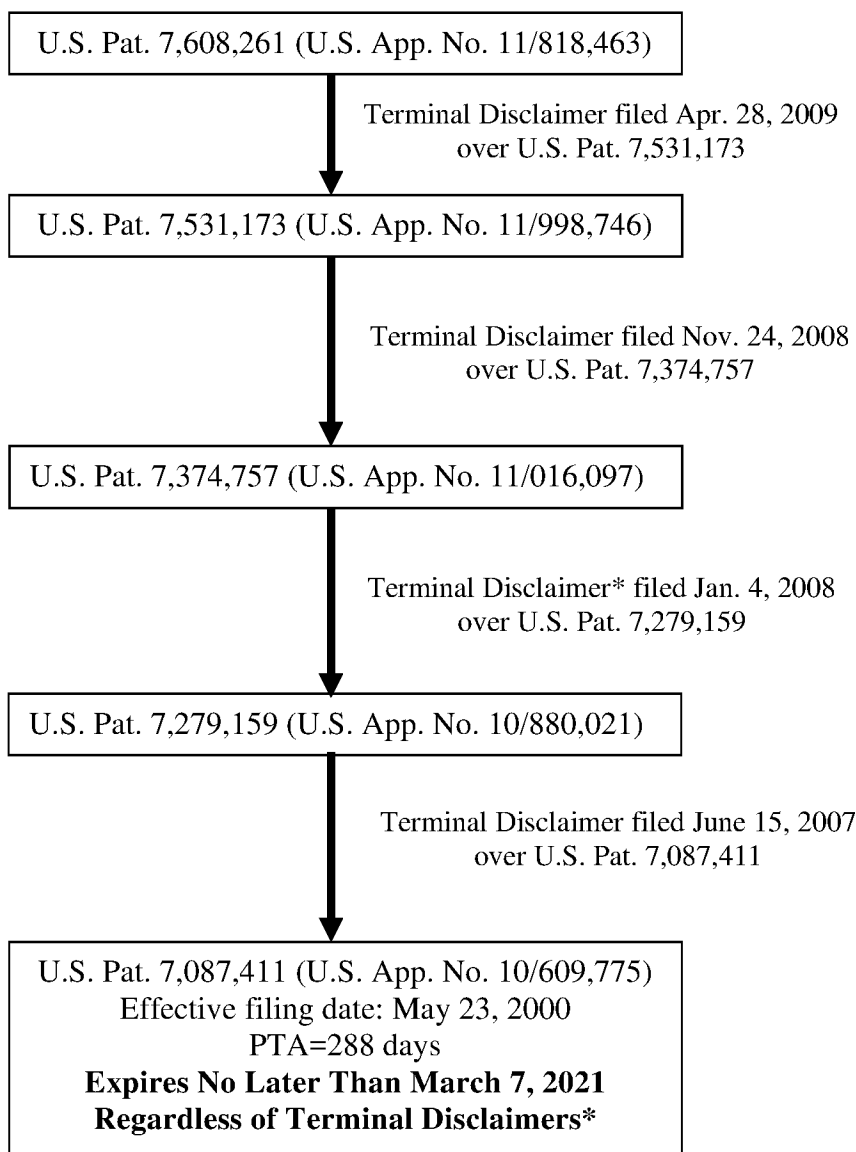
APPENDIX E – ALIGNMENT OF SEQ ID NO: 4 OF '992 PATENT AND SEQUENCE IN FIG. 24A-24C OF PAPADOPOULOS (WO'319, EXHIBIT 7)

100.0% identity in 458 residues overlap; Score: 2437.0; Gap frequency: 0.0%

WO319_FIG_24	1	MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTS
SeqID4-992	1	MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTGRELVIPCRVTS
WO319_FIG_24	61	PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIIISNATYKEIGLLTCEATVNGHLYKTNYLT
SeqID4-992	61	PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIIISNATYKEIGLLTCEATVNGHLYKTNYLT
WO319_FIG_24	121	HRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKLVNRD
SeqID4-992	121	HRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKLVNRD
WO319_FIG_24	181	LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPC
SeqID4-992	181	LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPC
WO319_FIG_24	241	PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
SeqID4-992	241	PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
WO319_FIG_24	301	KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
SeqID4-992	301	KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
WO319_FIG_24	361	TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSK
SeqID4-992	361	TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSK
WO319_FIG_24	421	LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SeqID4-992	421	LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

APPENDIX F – TERMINAL DISCLAIMER CHART

As shown below, the '261 Patent expires no later than March 7, 2021 due to its terminal disclaimer over U.S. Pat. 7,531,173. Each of the '594 and '489 Patents carries a terminal disclaimer over at the '261 Patent.



* The '757 and '411 Patents carry additional terminal disclaimers not analyzed here.