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90/014,448

02/11/2020

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04/01/2020

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EXAMINER

TURNER, SHARON L

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.



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***EX PARTE* REEXAMINATION COMMUNICATION TRANSMITTAL FORM**

REEXAMINATION CONTROL NO. 90/014,448 .

PATENT UNDER REEXAMINATION 10464992 .

ART UNIT 3991 .

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Order Granting Request For Ex Parte Reexamination	Control No. 90/014,448	Patent Under Reexamination 10464992	
	Examiner SHARON L TURNER	Art Unit 3991	AIA (FITF) Status No

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The request for *ex parte* reexamination filed 02/11/2020 has been considered and a determination has been made. An identification of the claims, the references relied upon, and the rationale supporting the determination are attached.

Attachments: a) ☐ PTO-892, b) ☒ PTO/SB/08, c) ☐ Other: _____

1. ☒ The request for *ex parte* reexamination is GRANTED.

RESPONSE TIMES ARE SET AS FOLLOWS:

For Patent Owner's Statement (Optional): TWO MONTHS from the mailing date of this communication (37 CFR 1.530 (b)). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**

For Requester's Reply (optional): TWO MONTHS from the **date of service** of any timely filed Patent Owner's Statement (37 CFR 1.535). **NO EXTENSION OF THIS TIME PERIOD IS PERMITTED.** If Patent Owner does not file a timely statement under 37 CFR 1.530(b), then no reply by requester is permitted.

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cc:Requester (if third party requester)

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

Ex Parte Reexamination

2. A Request for *Ex Parte* Reexamination (90/014,448, the ‘448 proceeding), of claims 1-18 (all) of U.S. Patent No. 10,464,992 (‘992) was filed 2/11/2020 by third party requester.

Scope of Reexamination

3. The reexamination proceeding provides a complete reexamination of the patent claims on the basis of prior art patents and printed publications (37 CFR 1.552, MPEP 2258).

Decision on Reexamination Request

4. A substantial new question of patentability (SNQ) affecting claims 1-18 of the ‘992 patent is raised by the request for reexamination.

Substantial New Question of Patentability

5. The presence or absence of “a substantial new question of patentability” (SNQ) determines whether or not reexamination is ordered.

For a “substantial new question of patentability” to be present, it is only necessary that:

A) the prior art patents and/or printed publications raise a substantial new question of patentability for at least one claim, such that a reasonable examiner would consider the teaching to be important in deciding whether or not the claim was patentable. A SNQ may be based on newly cited art or even solely on old art where the old art is being presented/viewed in a new light, or in a different way, as compared with its use in earlier concluded examination(s), in view of a material new argument or interpretation presented in the request. (MPEP 2242).

B) the same question of patentability as to the claim has not been decided by the Office in a previous examination or pending reexamination of the patent or in a final holding of invalidity by the Federal Courts, after appeals, or time for such have expired.

The '992 Patent and Claims

6. Instant 90/014,448, filed 02/11/2020 is a re-examination of 16/159,269, filed 10/12/2018, now U.S. Patent 10,464,992.

16/159,269 is a continuation of 15/879,294, filed 01/24/2018, now U.S. Patent 10,400,025.

15/879,294 is a continuation of 15/095,606, filed 04/11/2016, now U.S. Patent 9,914,763.

15/095,606 is a continuation of 14/330,096, filed 07/14/2014, now U.S. Patent 9,340,594.

14/330,096 is a continuation of 13/914,996, filed 06/11/2013, now U.S. Patent 8,802,107.

13/914,996 is a continuation of 13/329,770, filed 12/19/2011, now U.S. Patent 8,481,046.

13/329,770 is a continuation of 12/833,417, filed 07/09/2010, now U.S. Patent 8,092,803.

12/833,417 is a continuation of 12/560,885, filed 09/16/2009, now U.S. Patent 7,807,164.

12/560,885 is a division of 11/818,463, filed 06/14/2007, now U.S. Patent 7,608,261.

11/818,463 Claims Priority from Provisional Application 60/814,484, filed 06/16/2006.

The '992 patent consists of claims 1-18. Claims 1 and 10 are independent as appended below. Claims 2-9 and 11-18 depend directly or indirectly therefrom.

1. *A vial comprising:* a vascular endothelial growth factor (VEGF) antagonist, an organic co-solvent, a buffer, and a stabilizing agent, wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an 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.degree. C. for two months as measured by size exclusion chromatography.

10. *A formulation comprising:* a vascular endothelial growth factor (VEGF) antagonist, an organic co-solvent, a buffer, and a stabilizing agent, wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an 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.degree. C. for two months as measured by size exclusion chromatography.

Claim Interpretation

7. In making the determination of whether to order reexamination, the Office will determine the proper meaning of the patent claims by giving the claims their broadest reasonable interpretation consistent with the specification (see *In re Yamamoto*, 740 F.2d 1569 (Fed. Cir. 1984)). See MPEP 2240, 2258.

Documents Cited as Raising an SNQ

U.S. Patent No. 7,608,261 B2, issued on Oct. 27, 2009, to Furfine et al.

U.S. Patent No. 9,340,594 B2, issued on May 17, 2016, to Furfine et al.

U.S. Patent No. 9,580,489 B2, issued on Feb. 28, 2017, to Furfine et al.

Papadopoulos et al., International Patent Application Publication No. WO 00/75319 A1, published on Dec. 14, 2000 (Papadopoulos).

Baca et al., International Patent Application Publication No. WO 98/45331 A2, published on Oct. 15, 1998 (Baca).

Cunningham et al., International Patent Application Publication No. WO 00/63380 A1, published on Oct. 26, 2000 (Cunningham).

It is noted that the Request at p. 7, lines 1-4 notes that the Baca and Cunningham references are referred to as the “Exemplary Vial Pubs.” While this terminology is utilized within the request, the instant proceeding will refer to the cited teachings within the references individually.

Discussion of the Documents Cited as Raising an SNQ

8. The request proposes that a SNQ as to claims 1-18 is raised by claims 1-5 of the ‘594 patent in view of Papadopoulos, Baca and Cunningham (SNQ1 Request pp. 7, 13 and 22-36).

Claims 1-12 of the ‘594 patent were previously cited alone within the prosecution history within an obviousness-type double patenting rejection (see 16/159,269 Office Action 4/2/19). The rejection was overcome by amendments introducing elements relating to the percentage of VEGF antagonist which maintains conformation following storage over time (see 16/159,269

Response 7/22/19 and Notice of Allowance 8/21/19). Requester newly cites the teachings of claims 1-5 of the '594 patent with the teachings of Papadopoulos, Baca and Cunningham.

'594 claims 1-5 teach as follows:

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, 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, wherein the stable ophthalmic formulation comprises: (a) 1-100 mg/ml a VEGF antagonist; (b) 0.01-5% of one or more organic co-solvent; (c) 5-40 mM of buffer; and (d) optionally comprising 1.0-7.5% of a stabilizing agent.
2. The pre-filled syringe of claim 1, wherein the first VEGF receptor is Flt1, and the second VEGF receptor is Flk1 or Flt4.
3. The pre-filled syringe according to claim 2, wherein the VEGF trap is stable for at least 4 months.
4. The pre-filled syringe according to claim 3, wherein the VEGF trap consists of amino acids 27-457 of SEQ ID NO:4.
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.

Papadopoulos is newly cited and teaches modified chimeric polypeptides with improved pharmacokinetic properties, Title, Abstract, 28:2-29:6. In particular, the polypeptides are VEGF antagonists, including modified Flt1 receptors termed VEGFR1R2-Fc Δ C1(a), dimers, expression vectors and host cells for expression including CHO cells (12:10, 12:19-26, 22:1-2). Peptide mapping and glycosylation analysis shows peptides arrangements including in which the first two cysteines in the Fc region (211 and 214) form an intermolecular disulfide bond with the same two cysteines in another Fc chain (25:23-25). The reference also teaches the pharmacokinetics of Flt1(1-3)-Fc (A40), Flt1D2.FlklD3.Fc Δ C1(a) and VEGFR1R2- Fc Δ C1(a) (26:12-25). CHO cell culture production, harvest and purification of Flt1D2.FlklD3.Fc Δ C1(a) is taught in Example 21-22, particularly (67:25-68:5, 70:23-24). CHO transiently expressed Flt1 D2.FlklD3.Fc Δ C1(a), CHO stably expressed Flt1D2.FlklD3.Fc Δ C1 (a), and CHO transiently expressed VEGFR1R2-Fc Δ C1(a) is taught in Example 29, particularly (82:12-13), and corresponding sequences are taught in Fig. 24 A-C. These teachings are new non-cumulative technological features not previously discussed within the prosecution history and are relevant to VEGF antagonist compositions as recited within the '992 patent.

Baca is newly cited and teaches anti-VEGF antibodies and particularly containers and labels including syringes with compositions effective for treatment (Title, Abstract, 47:13-18). These teachings are new non-cumulative technological features not previously discussed within the prosecution history and are relevant to VEGF antagonist compositions as recited within the '992 patent.

Cunningham is newly cited and teaches VEGF variants and particularly containers and labels including syringes with compositions useful for diagnosing or treating conditions (Title, Abstract, 25:20-27). These teachings are new non-cumulative technological features not previously discussed within the prosecution history and are relevant to VEGF antagonist compositions as recited within the '992 patent.

The new non-cumulative technological features of Papadopolous, Baca and Cunningham present the teachings of claims 1-5 of the '594 patent in a new light and different way than previously discussed within the prosecution history. The new teachings are relevant to the vial compositions and formulations of claims 1-18 of the '992 patent and have not been previously addressed together within the prosecution history. There is a substantial likelihood that a reasonable examiner would consider these additional teachings together important in deciding whether the claims are patentable, and the same question of patentability has not been previously decided. Accordingly, the '594 patent with Papadopoulos, Baca and Cunningham raises a SNQ as to claims 1-18 of the '992 patent.

9. The request proposes that a SNQ as to claims 1-18 is raised by claims 1-5 of the '261 patent in view of Papadopoulos, Baca and Cunningham (SNQ2 Request pp. 7, 13 and 36-45).

Claims 1-15 and 17 of the '261 patent were previously cited alone within the prosecution history within an obviousness-type double patenting rejection (see 16/159,269 Office Action 4/2/19). The rejection was overcome by amendments introducing elements relating to the percentage of VEGF antagonist which maintains conformation following storage over time (see 16/159,269 Response 7/22/19 and Notice of Allowance 8/21/19). Requester newly cites the teachings of claims 1-5 of the '261 patent with the teachings of Papadopoulos, Baca and Cunningham.

'261 claims 1-5 teach as follows:

1. An ophthalmic formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising a) 1-100 mg/ml of a VEGF antagonist comprising the amino acid sequence of SEQ ID NO:4; 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; c) 30-150 mM of a tonicity agent selected from sodium chloride or potassium chloride; and, d) 5-40 mM of sodium phosphate buffer.
2. The ophthalmic formulation of claim 1, further comprising 1-7.5% of a stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, or mannitol, pH between about 5.8-7.0.
3. The ophthalmic formulation of claim 2, comprising about 1-100 mg/ml of the VEGF antagonist, 10 mM sodium phosphate buffer, 40 mM NaCl, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3.
4. The ophthalmic formulation of claim 3, comprising about 10-80 mg/ml of the VEGF antagonist.
5. The ophthalmic formulation of claim 4, 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.

The new non-cumulative teachings of Papadopoulos, Baca and Cunningham are addressed above.

The new non-cumulative technological features of Papadopoulos, Baca and Cunningham present the teachings of claims 1-5 of the '261 patent in a new light and different way than previously discussed within the prosecution history. The new teachings are relevant to the vial compositions and formulations of claims 1-18 of the '992 patent and have not been previously addressed together within the prosecution history. There is a substantial likelihood that a reasonable examiner would consider these additional teachings together important in deciding whether claims 1-18 were patentable, and the same question of patentability has not been

previously decided. Accordingly, the '261 patent with Papadopoulos, Baca and Cunningham raises a SNQ as to claims 1-18 of the '992 patent.

10. The request proposes that a SNQ as to claims 1-18 is raised by claims 1-29 of the '489 patent in view of Papadopoulos (SNQ3 Request pp. 13 and 45-53).

The '489 patent is newly cited and claims 1-29 teach as follows:

1. A formulation comprising: (a) 1-100 mg/mL of a VEGF-specific fusion protein antagonist; (b) 5-40 mM of a buffer; (c) 0.01-5% of an organic co-solvent; and (d) a stabilizer or 30-150 mM of a tonicity agent, wherein the VEGF-specific fusion protein antagonist represents at least 90% of the total weight of protein in the composition, at least 90% of the total weight of the VEGF-specific fusion protein antagonist is not present as an aggregate, and 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.
2. The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist represents at least 95% of the total weight of protein in the composition.
3. The formulation of claim 2, wherein the VEGF-specific fusion protein antagonist represents at least 99% of the total weight of protein in the composition.
4. The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist is present at a concentration of about 10 to about 80 mg/ml.
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.
6. The formulation of claim 1, wherein the buffer comprises a phosphate buffer.
7. The formulation of claim 6, wherein the buffer comprises sodium phosphate present at a concentration of 10 mM.
8. The formulation of claim 1, wherein the pH of the composition is about pH 5.8-7.0.
9. The formulation of claim 1, wherein the pH is about pH 6.2-6.3.
10. The formulation of claim 1, wherein the pH is about pH 6.0.
11. The formulation of claim 1, wherein the organic co-solvent comprises one or more of polysorbate 20, polysorbate 80, polyethylene glycol (PEG) 3350, and propylene glycol.
12. The formulation of claim 11, wherein the organic co-solvent is present at a concentration of 0.01-3%.
13. The formulation of claim 12, wherein the organic co-solvent is PEG 3350 or polypropylene glycol at a concentration of about 3%.
14. The formulation of claim 1, wherein the organic co-solvent is present at a concentration of 0.01-0.15%.
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%.
16. The formulation of claim 1, wherein the tonicity agent comprises sodium chloride or potassium chloride.
17. The formulation of claim 16, wherein the tonicity agent comprises sodium chloride present at a concentration of 20-135 mM.
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.
19. The formulation of claim 1, comprising a stabilizer comprising trehalose or sucrose.
20. The formulation of claim 19, wherein the stabilizer comprises sucrose.
21. The formulation of claim 20, wherein the sucrose is present at a concentration of 5%.
22. The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist does not comprise amino acids 1-26 of SEQ ID NO:4.
23. The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist is a dimer.
24. The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist is expressed in a Chinese hamster ovary (CHO) cell.

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.
26. A vial containing a formulation comprising: (a) 1-100 mg/mL of a VEGF-specific fusion protein antagonist; (b) 5-40 mM of a buffer; (c) 0.01-5% of an organic co-solvent; (d) a stabilizer or 30-150 mM of a tonicity agent, wherein the VEGF-specific fusion protein antagonist represents at least 90% of the total weight of protein in the composition, at least 90% of the total weight of the VEGF-specific fusion protein antagonist is not present as an aggregate, and the VEGF-specific fusion protein antagonist comprises an Ig domain 2 of human VEGF receptor 1, an Ig domain 3 of a human VEGF receptor 2, and a multimerizing component.
27. The vial of claim 26, wherein the composition is stored under an inert gas, wherein the inert gas is nitrogen, helium or argon.
28. The vial of claim 27, wherein the vial is stored at 5.degree. C.
29. The vial of claim 28, wherein the VEGF-specific fusion protein antagonist does not comprise amino acids 1-26 of SEQ ID NO:4.

The new non-cumulative teachings of Papadopoulos are addressed above.

These new non-cumulative technological features of the '489 patent claims and Papadopolous are relevant to claims 1-18 of the '992 patent and have not previously been discussed together within the prosecution history. There is a substantial likelihood that a reasonable examiner would consider these new teachings important in deciding whether claims 1-18 were patentable, and the same question of patentability has not been previously decided. Accordingly, the '489 patent with Papadopoulos raises a SNQ as to claims 1-18 of the '992 patent.

Conclusion

11. A substantial new question of patentability (SNQ) affecting claims 1-18 of the '992 patent is raised by the request for reexamination. Accordingly, Ex Parte reexamination is granted.

Amendment in Reexamination Proceedings

12. Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c).

Waiver of Right to file Patent Owner Statement

13. In a reexamination proceeding, Patent Owner may waive the right under 37 C.F.R. 1.530 to file a Patent Owner Statement. The document needs to contain a statement that Patent Owner waives the right under 37 C.F.R. 1.530 to file a Patent Owner Statement and proof of service in the manner provided by 37 C.F.R. 1.248, if the request for reexamination was made by a third party requester, see 37 C.F.R. 1.550(f).

Service of Papers

14. After the filing of a request for reexamination by a third party requester, any document filed by either the patent owner or the third party requester must be served on the other party (or parties where two or more third party requester proceedings are merged) in the reexamination proceeding in the manner provided by 37 CFR 1.248. See 37 CFR 1.550(f).

Extension of Time

15. Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to “an applicant” and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that ex parte reexamination proceedings “will be conducted with special dispatch” (37 CFR 1.550(a)). Extensions of time in ex parte reexamination proceedings are provided for in 37 CFR 1.550(c).

Duty to Disclose

16. The patent owner and requester are reminded of the continuing responsibility under 37 CFR 1.565(a), to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 10,464,992 throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Future Correspondence

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon Turner whose telephone number is 571-272-0894. The examiner can normally be reached on Monday through Thursday from 7:00 a.m. to 5:00 p.m. If the attempts to reach the examiner are unsuccessful, the examiner's supervisor, Tim Speer can be reached by dialing 313-446-4825. The official fax number for the organization where this application is assigned is 571-273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this *ex parte* reexamination proceeding should be directed as follows:

By EFS web: <https://efs.uspto.gov/efile/myportal/efs-registered>

By U.S. Postal Service Mail to:

Mail Stop *Ex Parte* Reexam
ATTN: Central Reexamination Unit
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