Trials@uspto.gov
571-272-7822

Paper No. 12
Date: June

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2025-00176
Patent 11,084,865 B2

Before SUSAN L. C. MITCHELL, MICHAEL A. VALEK, and JAMIE T. WISZ, *Administrative Patent Judges.*

VALEK, *Administrative Patent Judge.*

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Samsung Bioepis Co., Ltd. ("Petitioner") filed a Petition (Paper 2, "Pet."), seeking *inter partes* review of claims 1–12, 14–17, 19, 20, 22–36, 39–42, 44, 45, and 47–55 of U.S. Patent No. 11,084,865 B2 (Ex. 1001, "the '865 patent"). Regeneron Pharmaceuticals, Inc. ("Patent Owner") filed a Preliminary Response. Paper 8 ("Prelim. Resp.").

In its Preliminary Response, Patent Owner asks that we exercise discretion to deny institution under 35 U.S.C. § 314(a) in view of parallel district court litigation involving the '865 patent. *See* Prelim. Resp. 6–17. With our authorization, Petitioner filed a reply to Patent Owner's arguments for discretionary denial under § 314(a) (Paper 10 ("Reply")) and Patent Owner filed a sur-reply (Paper 11 ("Sur-reply")).

For the reasons set forth below, we exercise discretion under 35 U.S.C. § 314(a) to deny institution of the Petition.

II. BACKGROUND

A. Real Parties in Interest

Petitioner and Patent Owner identify themselves as the only real parties in interest. Pet. 6; Paper 6, 1.

B. Related Matters

The '865 patent is currently asserted against Petitioner in *Regeneron Pharmaceuticals, Inc. v. Samsung Bioepis Co., Ltd.*, No. 1:23-cv-106 (N.D.W. Va.) and *Regeneron Pharmaceuticals, Inc. v. Samsung Bioepis Co., Ltd.*, No. 1:23-cv-94 (N.D.W. Va.). Pet. 6–7. The '865 patent has been asserted against a number of other defendants in the following matters:

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Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc., No. 1:22-cv-61 (N.D.W. Va.) ("the Mylan case"); *Regeneron Pharmaceuticals, Inc. v. Formycon AG*, No. 1:23-cv-97 (N.D.W. Va.); *Regeneron Pharmaceuticals, Inc. v. Celltrion, Inc.*, Nos. 1:23-cv-89, 1:24-cv-53 (N.D.W. Va.); *Regeneron Pharmaceuticals, Inc. v. Amgen Inc.*, No. 2:24-cv-264 (C.D. Cal.); *Regeneron Pharmaceuticals, Inc. v. Sandoz Inc.*, No. 3:24-cv-876 (D.N.J.). Paper 6, 1–4. According to Patent Owner, "[t]he U.S. Judicial Panel on Multidistrict Litigation instituted a multidistrict litigation incorporating the aforementioned actions in the Northern District of West Virginia." *Id.* at 2. We refer to these cases collectively as "the MDL proceeding" and the cases against Petitioner specifically as "the SB case."

The first of these cases, the Mylan case, has already proceeded through trial. Following a 9-day bench trial, the district court issued a detailed opinion finding that Mylan[1] infringed claims 4, 7, 9, 11, and 14–17 of the '865 patent and had not shown that those claims are invalid under 35 U.S.C. §§ 102, 103, or 112. Ex. 2001 ("Mylan Decision"), 3, 311–312. The district court's judgment was appealed and later that appeal was dismissed by joint stipulation as part of agreement between Mylan and Patent Owner resolving their disputes. *See* Reply 2, n. 1; Ex. 1138, 1–2 (April 22, 2025 order entering joint stipulation and order offered by Patent Owner and Mylan).

The district court has also conducted preliminary injunction ("PI") proceedings and granted PIs based on the '865 patent against Petitioner and two other biosimilar applicant defendants in the MDL proceeding. Ex. 2002

[1] Mylan Pharmaceuticals Inc. and Biocon Biologics Inc. are joint defendants in this case. *See* Ex. 2001, 1. Here, we refer to them collectively as "Mylan."

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(order granting motion for preliminary injunction against Samsung Bioepis) ("SB PI order"); *see also* Ex. 2003 (order granting motion for preliminary injunction against Formycon) ("Formycon PI order"); Ex. 2004 (order granting motion for preliminary injunction against Celltrion) ("Celltrion PI order"). Each of those decisions was appealed and recently affirmed by the Federal Circuit. *See* Ex. 2005–2007. The district court also considered and denied Patent Owner's motion for a preliminary injunction against Amgen. Paper 6, 3. According to Patent Owner, the Amgen PI motion was denied because the district court found it "was not likely to succeed on infringement." *Id.*

The '865 patent is also the subject of petitions for *inter partes* review filed by other defendants in the MDL proceeding, i.e., IPR2025-00233 ("the Formycon IPR") and IPR2025-00456 ("the Celltrion IPR"). The petition in the Formycon IPR is a "copycat" of the Petition here, filed along with a motion for joinder. IPR2025-00233, Paper 2, 1. The petition in the Celltrion IPR raises different grounds of unpatentability for a largely overlapping set of challenged claims. *Compare* IPR2025-00456, Paper 2, 21, *with* Pet. 10 (identifying different grounds of unpatentability).

In addition, the parties identify IPR2021-00402, IPR2023-01312, and IPR2023-00462 as matters involving U.S. Patent No. 10,464,992 B2, which is related to the '865 patent. Pet. 6; Paper 6, 4–5; *see also* Ex. 1001, code (60).

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C. The '865 Patent

The '865 patent issued on August 10, 2021, and claims priority to a series of applications, the earliest of which was filed on June 16, 2006. Ex. 1001, codes (45), (60).

The '865 patent relates to "pharmaceutical formulations suitable for intravitreal administration comprising agents capable of inhibiting vascular endothelial growth factor (VEGF), and to methods for making and using such formulations." Ex. 1001, 1:45–49. According to the Specification, "[a] VEGF antagonist is a compound capable of blocking or inhibiting the biological action of vascular endothelial growth factor (VEGF), and includes fusion proteins capable of trapping VEGF." *Id.* at 6:27–30. Relevant to the claims challenged here, "the fusion protein comprises amino acids 27-457 of SEQ ID NO:4." *Id.* at 6:34–37. The parties refer to the fusion protein comprising this amino acid sequence as aflibercept. *See, e.g.*, Pet. 38; Prelim. Resp. 28, 32, 39 (referring to the "aflibercept amino acid sequence"). According to the Specification, in "a specific embodiment" this protein is "glycosylated at Asn residues 62, 94, 149, 222 and 308." Ex. 1001, 6:35–37.[2]

The '865 patent describes a "stable liquid ophthalmic formulation" comprising aflibercept, one or more organic co-solvents, e.g., polysorbate, one or more tonicity agents, e.g., sodium or potassium chloride, a buffering agent, e.g., phosphate buffer, and a stabilizing agent, e.g., sucrose, in varying

[2] According to Petitioner's declarant, "glycosylation refers to the process by which 'glycans' are created, altered, and attached to proteins," and because the '865 patent describes glycosylation at asparagine residues, it is referring to "N-linked glycosylation," i.e., "glycans attached to the side-chain nitrogen atoms of asparagine residues." Ex. 1007 ¶¶ 27–29.

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amounts. *See id.* at 2:33–4:6. Such formulations may be "provided in a pre-filled syringe or vial, particularly suitable for intravitreal administration." *Id.* at 5:23–25.

D. Challenged Claims

The Petition challenges claims 1–12, 14–17, 19, 20, 22–36, 39–42, 44, 45, and 47–55. Pet. 9. Of these, claims 1, 26, and 51 are independent. Claim 1 is illustrative and reads as follows:

> 1. A vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises:
> a vascular endothelial growth factor (VEGF) antagonist
> an organic co-solvent,
> a buffer, and
> a stabilizing agent,
> wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4; 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.

Ex. 1001, 19:29–40, 22:18–30. Claim 26 is nearly identical to claim 1, but recites the formulation in a "pre-filled syringe" instead of a vial. *Id.* at 20:66–21:12. Claims 2 and 27 depend from claims 1 and 26 respectively and further recite that the concentration of VEGF antagonist fusion protein is "40 mg/ml" and that the co-solvent comprises polysorbate. *Id.* at 19:41–43, 21:13–16. Claim 51 recites a similar ophthalmic formulation with the same limitations requiring, *inter alia*, that the VEGF antagonist fusion protein be glycosylated and have a 40 mg/ml concentration. *Id.* at 22:19–31.

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E. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claim(s) Challenged	35 U.S.C. §[3]	Reference(s)/Basis
1–12, 14–17, 19, 20, 22–25, 51–53, 55	103(a)	Fraser,[4] Wulff,[5] 2006 Presentations,[6] '319 Publication,[7] FDA Guidance[8]
26–36, 39–42, 44, 45, 47–50, 54	103(a)	Fraser, Wulff, 2006 Presentations, '319 Publication, Nayar[9]

[3] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), included revisions to 35 U.S.C. § 103 that became effective after the filing of the applications to which the '865 patent claims priority. Therefore, we apply the pre-AIA version of 35 U.S.C. § 103.

[4] Fraser et al., "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function," 90(2) J. Clin. Endocrinol. Metab. 1114–22 (2005) (Ex. 1009) ("Fraser").

[5] Wulff et al., "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2," 143(7) Endocrinology 2797–807 (2002) (Ex. 1016) ("Wulff").

[6] The Petition refers to the three presentations in Exhibits 1011–1013, which were apparently obtained from the Internet Archive's Wayback Machine, as the "2006 Presentations." *See* Pet. 26–27.

[7] WO 00/75319 A1, published December 14, 2000 (Ex. 1029) ("'319 Publication").

[8] U.S. Dept. of Health and Human Serv., "Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics" (May 1999) (Ex. 1038) ("FDA Guidance").

[9] Rajiv Nayar & Mark C. Manning, *High Throughput Formulation: Strategies for Rapid Development of Stable Protein Products*, *in* RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS: THEORY AND PRACTICE (John F. Carpenter & Mark C. Manning eds., 2002) (Ex. 1020) ("Nayar").

Petitioner further relies on the declarations of Dr. Alpaslan Yaman (Ex. 1002), Dr. Edward Chaum (Ex. 1005), and Dr. Michael Butler (Ex. 1007) submitted with the Petition.

III. DISCRETION UNDER 35 U.S.C. § 314(A)

We begin by addressing Patent Owner's arguments for discretionary denial. As explained below, we find those arguments persuasive. Thus, we exercise discretion to deny institution of the Petition under 35 U.S.C. § 314(a) without reaching the merits of Petitioner's asserted grounds of unpatentability.

A. The Parties' Arguments

Patent Owner argues that we should exercise discretion under 35 U.S.C. § 314(a) to deny institution of *inter partes* review in view of the Mylan case and related MDL proceeding. Prelim. Resp. 6–17. In particular, Patent Owner argues the Petition was filed 365 days after Petitioner was sued and "implicates the same or substantially similar claims, prior-art references, and issues that have been decided repeatedly by the district court and the Federal Circuit" in "seven court decisions."[10] *Id.* at 6–7. According to Patent Owner, these decisions contain "hundreds of pages" on obviousness and obviousness-type double patenting ("ODP") addressing disputes that overlap with the issues raised in the Petition, and that "[g]iven

[10] The seven decisions Patent Owner refers to are the district court's bench trial opinion in the Mylan case (Ex. 2001), the district court's three orders granting Patent Owner's motions for preliminary injunction against Petitioner, Formycon, and Celltrion (Ex. 2002–2004), and the Federal Circuit's three decisions affirming those preliminary injunction orders (Ex. 2005–2007). *See* Prelim. Resp. 1.

the considerable investment of the parties and the courts in these proceedings, institution would be highly inefficient." *Id.* For these and other reasons, Patent Owner urges that the *Fintiv*[11] factors favor the exercise of discretion to deny institution under § 314(a). *Id.* at 6–17.

Petitioner disputes Patent Owner's assessment of the *Fintiv* factors and contends these factors do not favor the exercise of discretion to deny institution. *See* Pet. 69–70; Reply 1–2, 8–10. In particular, Petitioner contends the obviousness grounds in the Petition "rely on a combination of three primary references—*Fraser*, *Wulff*, and the *2006 Presentations*—that has never been previously asserted and was not the subject of any prior decision." Reply 4. Petitioner also points out that no trial date has been set in its district court case. *Id.* at 8. Moreover, in an attempt to "avoid any risk of overlap or duplication," Petitioner stipulates that if institution is granted: (1) it "will not pursue an invalidity defense in the parallel litigations . . . that the claims subject to the instituted IPR are invalid based on the grounds that were raised or any grounds Petitioner reasonably could have raised in this IPR," i.e., a *Sotera*[12] stipulation; and (2) "it will not seek a trial date on the '865 patent before the FWD is due." *Id.* at 9–10. Finally, Petitioner contends

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[11] *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential) ("*Fintiv*").

[12] *Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 (PTAB Dec. 1, 2020) (precedential as to § II.A.) ("*Sotera*"). Petitioner's stipulation differs from that in *Sotera* because Petitioner limits it to just "the claims subject to the instituted IPR," which suggests its stipulation would apply only to the subset of the'865 patent's claims challenged in the Petition. *Compare* Reply 10, *with Sotera* 18. For sake of argument, we do not address this distinction because it does not affect the outcome of the *Fintiv* analysis here.

it did not delay in filing the Petition because Patent Owner "did not serve Petitioner with the complaint until October 16, 2024" and "Petitioner filed its Petition just one month later, after it became clear the district court did not intend to act quickly." *Id.* at 10.

Patent Owner responds, reiterating its position that the disputed issues in this proceeding are the same or substantially similar to those the district court and Federal Circuit have already addressed and resolved in its favor. *See* Sur-reply 1–9. Patent Owner further contends that Petitioner's *Sotera* stipulation does not mitigate concerns with duplication, and "[t]he current lack of a scheduled trial date does not outweigh the massive overlap with and investment in the parallel proceedings." *Id.* at 9–10.

B. The Fintiv Factors and Related Guidance

The Board's precedential decision in *Fintiv* outlines factors that balance considerations of system efficiency, fairness, and patent quality when a patent owner raises an argument for discretionary denial due to the advanced state of a parallel proceeding, such as the MDL proceeding here. *Fintiv* 5–6. These factors are:

> 1. whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
>
> 2. proximity of the court's trial date to the Board's projected statutory deadline for a final written decision;
>
> 3. investment in the parallel proceeding by the court and the parties;
>
> 4. overlap between issues raised in the petition and in the parallel proceeding;

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> 5. whether the petitioner and the defendant in the parallel proceeding are the same party; and
>
> 6. other circumstances that impact the Board's exercise of discretion, including the merits.

Id. "[I]n evaluating the factors, the Board takes a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review." *Id.* at 6.

The Office recently rescinded an earlier memorandum titled "Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation," and offered new guidance regarding the *Fintiv* analysis.[13] This guidance states that the recission "restore[s] policy in this area to the guidance in place before the Interim Procedure," including by making clear that a *Sotera* "stipulation (*i.e.*, a stipulation from a petitioner that, if an IPR or PGR is instituted, the petitioner will not pursue in district court . . . any ground raised or that could have been reasonably raised in the IPR/PGR) is highly relevant, but will not be dispositive by itself" and that "compelling merits alone is not dispositive." Guidance Memo, 1–3.

C. Analysis

We now consider these factors to assess whether to exercise discretion to deny institution under 35 U.S.C. § 314(a) in this case.

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[13] Memorandum from the Chief Administrative Patent Judge, *Guidance on USPTO's recission of "Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation* (March 24, 2025), available at https://www.uspto.gov/sites/default/files/documents/guidance_memo_on_interim_procedure_recission_20250324.pdf ("Guidance Memo"), 1.

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i. Factor 1: likelihood of a stay in the MDL proceeding

No stay has been granted, nor is there any evidence of record that either party has asked for one. Moreover, Patent Owner represents that it "does not intend to seek a stay." Prelim. Resp. 15.

Petitioner does not address whether it would seek a stay if institution were granted. But the fact that Petitioner is presently enjoined from launching its biosimilar product (*see* Ex. 2005, 3) and that it has repeatedly sought the entry of a schedule with an earlier trial date than that proposed by Patent Owner (*see* Ex. 1110, 1135), suggests Petitioner is unlikely to seek a stay.

It is possible the parties could change their minds or that the district court could enter a stay *sua sponte*. However, that possibility seems remote given our understanding that the MDL proceeding involves a number of Patent Owner's other patents and also several other biosimilar applicant defendants who may seek to raise different issues than those presented here. In any event, we decline to give substantial weight to such speculation. Accordingly, this factor is neutral.

ii. Factor 2: proximity of the trial date to the final written decision deadline

The projected statutory deadline for a final written decision in this case is one year after the entry of this decision, i.e., in June 2026.

We understand a trial date has not yet been set for the SB case or any of the other pending cases in the MDL proceeding. *See* Sur-reply 10 (acknowledging "[t]he current lack of a scheduled trial date"). According to Petitioner, the SB case has been "stagnant" or "essentially stayed" since at

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least the time when the PI proceeding ended and the SB PI Order was entered in June 2024. *See* Reply 3.[14]

Patent Owner suggests the delay in entering a schedule following issuance of the SB PI Order (and the district court's subsequent PI orders) was to allow time for the appeals of those decisions and for the Mylan Decision to be resolved. *See* Prelim. Resp. 16 (explaining that while Petitioner sought an earlier trial schedule, Patent Owner "proposed that the district court convene a status conference upon resolution of the remaining pending appeals and then determine an appropriate schedule"). "Given the conclusion of the appeals," the parties in the MDL proceeding have now jointly requested "an in-person status conference" with the district court "to set a case schedule for further proceedings." Ex. 2035, 1 (email on behalf of all parties to the MDL proceeding dated April 30, 2025). Thus, the parties in the MDL proceeding appear to be working toward entry of a trial schedule.

Nevertheless, at present, there is no set trial date and outside of the now-completed PI proceedings, no schedule has been set in the MDL proceeding. This suggests that the trial in the SB case may occur after the projected statutory deadline of June 2026. For this reason, factor 2 weighs against discretionary denial.

[14] Petitioner asserts the district court case has been stagnant for "20 months." Reply 3. Petitioner's math is hard to follow given that the first SB case was filed in November 2023, less than 20 months ago. SB PI Order 8. To the extent Petitioner suggests nothing has happened in the MDL proceeding since the SB case was filed, we disagree, because that suggestion ignores the substantial investment the district court and parties have made in litigating the PI proceedings and subsequent appeals.

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But we disagree with Petitioner that this factor alone is dispositive. According to Petitioner, in the absence of a trial date there is no need to engage in a full *Fintiv* analysis because there is no basis for discretionary denial. Reply 8 (citing *Beckman Coulter, Inc. v. Sirigen II Ltd.*, IPR2022-01203, Paper 12, 18 (PTAB Jan. 6, 2023)). This is a bridge too far. "[T]he factors considered in the exercise of discretion are part of a balanced assessment of all the relevant circumstances in the case." *See* Guidance Memo, 3 (explaining that for this reason "compelling merits alone is not dispositive"). Because the *Fintiv* factors are considered together as part of a "holistic" analysis, we decline Petitioner's invitation to cut the *Fintiv* analysis short here by only considering the current lack of a trial date under factor 2. *See Fintiv* 6.

iii. Factor 3: investment in the parallel proceedings

Patent Owner asserts that the district court's consideration and grant of the PI against Petitioner alone constitutes a substantial investment, but that the district court did even more by conducting "a two-week trial in the *Mylan* case and three other preliminary-injunction proceedings focused on validity of the '865 patent." Prelim. Resp. 8. We agree.

Just within the context of the PI proceeding involving Petitioner, the district court considered testimony from seven different witnesses. *See* SB PI Order 13 (identifying witnesses).[15] It issued a thorough 181-page decision with voluminous citations to the record evidence, including more than 50

[15] The parties waived an evidentiary hearing, so the PI motion was decided on written submissions. SB PI Order, 12–13. Direct testimony was submitted in the form of declarations and both sides conducted cross-examination by deposition, which the district court also considered. *Id.* at 13; *see, e.g.*, *id.* at 48, 87–88, 143 (citing transcripts).

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pages addressing Petitioner's ODP defense. *Id.* at 54–110. As explained in more detail below, that ODP defense presents a number of disputed issues that are the same or substantially similar to the disputed issues in this proceeding. On the preliminary record, the district court resolved those issues in Patent Owner's favor, finding that Petitioner had not raised a substantial question of validity. *Id.* at 54. The Federal Circuit affirmed that decision. Ex. 2005. The effort taken to litigate and decide the myriad issues raised by Patent Owner and Petitioner's PI filings demonstrates a substantial investment by the district court and the parties.

But this is far from the only substantial investment the district court has made. The district court completed claim construction proceedings and a full trial on the '865 patent in the Mylan case, issuing a more than 300-page trial decision.[16] That decision includes analysis of obviousness defenses based on one of the references (Fraser) in Petitioner's grounds and extensive fact-finding regarding Fraser and other references (e.g., Ex. 1029; Ex. 1039) that both sides rely on to support their positions in this proceeding. *See* Mylan Dec. 170–202. Moreover, the district court analyzed and credited the same objective indicia arguments Patent Owner raises here. *Id.* at 194–202; *see* Prelim. Resp. 60–63 (discussing objective indicia of non-obviousness).

In addition, the district court has decided PI motions based on the '865 patent for three other biosimilar applicants in the MDL proceeding. *See* Paper 6, 3. Similar to the SB PI Order, the district court's decisions

[16] While the district court agreed to vacate its final judgment and order for injunctive relief against Mylan in light of a settlement agreement between the parties, the trial decision itself was not vacated. *See* Ex. 1138, 2. Even if it had been, this would not diminish the district court's extensive investment in that proceeding.

granting preliminary injunctions against Formycon and Celltrion involve lengthy analysis of an ODP defense that overlaps with several of the disputed issues here. *See* Formycon PI Order 69–129; Celltrion PI Order 61–118 (analyzing ODP). These decisions were likewise affirmed by the Federal Circuit. Ex. 2006; Ex. 2007. All told, the district court's substantive decisions in the MDL proceeding to date total almost a thousand pages, much of it directed to issues relating to claim construction and the validity of the '865 patent claims.

There is also the issue of Petitioner's delay in filing the Petition. The Petition was filed on November 20, 2024, about a year after the filing of the first SB case before the district court. According to Petitioner, the complaint in the SB case was not *served* until October 16, 2024. Reply 10. But this does not explain why Petitioner waited a year after it was sued to initiate this proceeding challenging the '865 patent. Petitioner points out that there are "40+ patents" asserted in the SB case. *Id.* at 1. However, Patent Owner's PI motion was filed on February 22, 2024 and asserts only four patents.[17] That motion also identifies a particular subset of the '865 patent's dependent claims Petitioner is accused of infringing. SB PI Order 9; *see also Fintiv* 11 ("[I]t is often reasonable for a petitioner to wait to file its petition until it learns which claims are being asserted against it."). Thus, Petitioner was aware of the particular claims being asserted against it as early as February 2024 and could have filed a Petition challenging them far earlier than it did.

[17] Patent Owner later withdrew its motion with respect to three of those patents, limiting it to just the '865 patent. *See* SB PI Order 9 (stating Patent Owner did this to "streamline the issues in dispute").

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Petitioner's delay in doing so is another fact in favor of denial.[18] *See Fintiv* 11–12 (explaining that if "petitioner did not file the petition expeditiously" or "cannot explain the delay. . . these facts have favored denial").

For these reasons, factor 3 weighs heavily in favor of discretionary denial.

iv. Factor 4: overlap in issues

Patent Owner asserts that *Fintiv* factor four "weighs heavily in favor of discretionary denial" because the issues in the Petition substantially overlap with the MDL proceeding. Prelim. Resp. 11–15 (citing Pet. 1, 18 n.1, 23–30, 33–66, 69–70). Specifically, Patent Owner contends that, like Petitioner here, the defendants in the MDL proceeding have asserted that: (1) one of ordinary skill would have "had motivation to use 40 mg/mL aflibercept in an ophthalmic formulation"; (2) "aflibercept is necessarily glycosylated;" (3) "98% native conformation is inherent in formulations with the ingredients, concentrations, and pH recited by the claims [and] that the POSA was motivated with a reasonable expectation of success to make formulations with 98% native conformation;" and (4) "no objective evidence supported nonobviousness." Prelim. Resp. 14.

We agree these arguments are the same or similar to the arguments in the Petition. *See* Pet. 49–51 (arguing one of ordinary skill would have been

[18] Petitioner claims it was "forced to limit its defenses" in view of the page limit for its opposition to the preliminary injunction motion and "accordingly did not raise any obviousness combinations as to the '865 patent during the PI proceedings." Reply 1, 10. But that begs the question: if Petitioner believed it could not effectively raise the grounds in the Petition in its opposition to the PI, why did it wait 9 months after the PI motion was filed and 5 months after the SB PI Order was entered to file the Petition?

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motivated to set the concentration at 40 mg/ml), 38–41 (arguing that even though the asserted references do "not expressly teach glycosylated aflibercept" Wulff and the '319 publication teach expression in Chinese Hamster Ovary ("CHO") cells, which a skilled artisan would have known would result in the glycosylated protein); 40–48 (arguing that the claimed 98% native conformation after two months is inherent and/or obvious); 62–63 (arguing there are no objective indicia of non-obviousness for lack of nexus).

We also agree with Patent Owner that the district court made a number of fact findings in the SB PI Order and Mylan Decision that bear on these arguments, even though the grounds in the Petition are based on different combinations of art. *See* Prelim. Resp. 14–15 (identifying specific findings). For example, in the Mylan case, the district court found that the prior art taught away from the claimed 40 mg/ml concentration. Mylan Dec. 172–179. It also found that "objective evidence strongly supports nonobviousness" and that Patent Owner had established a sufficient nexus between that evidence and the '865 patent claims. *Id.* at 194–202; *see also* SB PI Order 108–110 (similar). Moreover, in the PI proceeding, the district court found that "aflibercept is not necessarily glycosylated" even when produced in a CHO cell and that one of ordinary skill in the art would not be motivated to use the glycosylated form of the protein in an ophthalmic formulation. SB PI Order 79–91; *see also* Ex. 2005, 22–23 (noting on appeal that "SB does not challenge . . . the district's finding that a relevant artisan lacked the motivation to use glycosylated aflibercept because such an artisan would know that glycosylation would increase the size of aflibercept, which

would hamper retinal penetration . . . and increase risks such as inflammation").

Petitioner attempts to distinguish these and other findings from the district court by pointing to teachings in some of its cited references that differ from those considered in the Mylan case and the reference claims in Petitioner's ODP defense. *See* Reply 3–8. Those differences, however, appear to be relatively minor on the record before us. At most, they show that some of the disputed issues that have already been considered by the district court in its Mylan Decision and PI Orders, and that remain before it now in those cases still pending in the MDL proceeding, are substantially similar, as opposed to identical, to the disputed issues in the Petition. Either way, there is substantial overlap between the issues both previously litigated and currently pending in the district court and the grounds in the Petition.

The *Sotera* stipulation is an attempt to counterbalance the concerns raised by this overlap, but given the circumstances, it does not effectively mitigate them. First, the disputed issues for Petitioner's ODP defense are the same or substantially similar to those for the obviousness grounds in the Petition, but the *Sotera* stipulation does not prevent Petitioner from litigating those issues before both the district court (as part of its ODP defense) and here in the event an IPR is instituted.[19] Second, the MDL proceeding

[19] ODP or nonstatutory double patenting is, as the name implies, not premised on any statute. *See, e.g.*, *Ostuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1297 (Fed. Cir. 2012) ("Nonstatutory double patenting is a judicially created doctrine grounded in public policy."). Accordingly, it is *not* a ground Petitioner reasonably could have raised in this IPR. *See* 35 U.S.C. § 311(b) (inter partes review may be requested "only on a ground that could be raised under section 102 or 103").

includes other biosimilar applicant defendants who are similarly motivated to try to invalidate the '865 patent claims, but who are not subject to any *Sotera* stipulation. Even if we institute review on Petitioner's grounds here, those other defendants remain free to litigate the same grounds in the consolidated MDL proceeding. For these reasons and given the particular circumstances of this case, Petitioner's *Sotera* stipulation does not sufficiently mitigate the risks of duplicated efforts or inconsistent decisions by making this IPR a "true alternative" to resolution of these issues by the district court. *See Motorola Solutions, Inc. v. Stellar, LLC,* IPR2024-01205, Paper 19, 3–4 (PTAB Mar. 28, 2005) (determining on Director Review that a *Sotera* stipulation did not ensure IPR would be a "true alternative" because Petitioner's invalidity arguments "include combinations of the prior art asserted in these proceedings with unpublished system prior art, which Petitioner's stipulation is not likely to moot" and thus the same or similar issues would remain in the parallel proceeding); *SAP America, Inc. v. Cyandia, Inc.*, IPR2024-01496, Paper 13, 8–9 (PTAB Apr. 7, 2025) (similar).

Finally, while the Petition appears to challenge a broader set of claims than those asserted in the SB case, that difference does not materially affect the overlap. The claims challenged in the Petition collectively raise the same disputed and overlapping issues identified above.

For these reasons, factor 4 weighs in favor of discretionary denial.

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v. Factor 5: same or different parties

Petitioner and Patent Owner are both parties to the MDL proceeding. Therefore, this factor weighs in favor of exercising discretion to deny the Petition.

vi. Factor 6: other circumstances, including the merits

This factor accounts for other relevant circumstances, including whether "the merits of a ground raised in the petition seem particularly strong on the preliminary record," which favors institution. *Fintiv* 14–15. "By contrast, if the merits of the grounds raised in the petition are a closer call, then that fact has favored denying institution when other factors favoring denial are present." *Id.* at 15.

The merits in this case are in the latter category, particularly as they relate to the limitations requiring an "ophthalmic formulation" containing "glycosylated" aflibercept. *See, e.g.*, Ex. 1001, 19:29–37 (claim 1). Based on the record in the PI proceeding, the district court found that one of ordinary skill in the art would not have been motivated to use glycosylated aflibercept in an ophthalmic formulation for several reasons, including that the larger glycosylated form of the protein would reduce retinal penetration, undesirably increase systemic exposure, and increase the risk of inflammation. SB PI Order 84–91. Petitioner did not challenge that finding on appeal. Ex. 2005, 22. Nevertheless, Petitioner ignores the substance of the district court's reasoning and the supporting evidence cited by Patent Owner in its Preliminary Response. Instead, Petitioner contends:

> Petitioner need not show motivation to glycosylate aflibercept because [it] relies on prior art that the POSA would understand discloses glycosylated aflibercept. Specifically the *Wulff*

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> reference teaches the VEGF trap was expressed in CHO cells, which by the priority date, were known and expected to glycosylate aflibercept. . . . Thus, a POSA would have understood the aflibercept disclosed in the primary reference (*Wulff*) ***was*** glycosylated—no motivation is needed to do more.

Reply 5 (internal quotations/citations omitted).

In our view, Petitioner's response is unsatisfactory because the challenged claims require more than just glycosylated aflibercept—they require glycosylated aflibercept in "an ophthalmic formulation suitable for intravitreal administration." *See, e.g.*, Ex. 1001, 19:29–30 (claim 1). Petitioner concedes Wulff does not disclose the use of its VEGF trap in an ophthalmic formulation, urging instead that one of skill in the art would have been motivated to make changes to Fraser and Wulff's intravenous formulation to convert it to an intravitreal one. *See* Pet. 30–35. But it appears to be undisputed that one of ordinary skill in the art would have understood that aflibercept could be produced in either a glycosylated or unglycosylated form. SB PI Order 79 ("As explained by experts on both sides, aflibercept . . . can be produced from different cells, only some of which result in glycosylation of aflibercept."); *see also* Ex. 1029 (teaching expression in systems other than CHO cells); Ex. 1039 ¶ 38 (teaching glycosylation may be eliminated by using mutant CHO cell lines). Accordingly, to demonstrate that the claimed ophthalmic formulation is obvious, Petitioner would need to articulate some reasoning to explain why one of ordinary skill in the art would choose to use the glycosylated version in that formulation. The fact that Petitioner elected not to mention, much less attempt to address the substance of the district court's findings that such a

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motivation was lacking, suggests a weakness in this aspect of its asserted grounds.[20]

For these reasons, factor 6 weighs in favor of discretionary denial.

D. Weighing of Fintiv Factors

Considering the *Fintiv* factors as part of a holistic analysis of all of the relevant circumstances of this case, we are persuaded that the interests of the efficiency and integrity of the system are served by invoking our authority under 35 U.S.C. § 314(a) to deny institution of a potentially meritorious Petition. That is, while the lack of a trial date (factor 2) weighs against denial, that single factor is solidly outweighed by the sum of the others, particularly factors 3, 4, and 6, which reflect the substantial investment in, and particular circumstances of, the parallel district court proceedings.

IV. CONCLUSION

For the foregoing reasons, we exercise discretion under 35 U.S.C. § 314(a) to deny the Petition.

V. ORDER

Accordingly, it is:

ORDERED that the Petition is denied, and no *inter partes* review is instituted.

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[20] We also have concerns regarding Petitioner's decision not to address the district court's prior finding that the art taught away from a 40 mg/ml concentration (*see* Mylan Dec. 172–179) and what that may signal regarding the relative strength of Petitioner's arguments regarding that limitation. That limitation, however, is recited in only a subset of the challenged claims.

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For PETITIONER:

Raymond N. Nimrod
Landon A. Smith
QUINN, EMANUEL, URQUHART & SULLIVAN, LLP
raynimrod@quinnemanuel.com
landonsmith@quinnemanuel.com

For PATENT OWNER:

David I. Berl
Andrew V. Trask
Arthur J. Argall
WILLIAMS & CONNOLLY LLP
dberl@wc.com
atrask@wc.com
aargall@wc.com

Elizabeth S. Weiswasser
Priyata Y. Patel
PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP
eweiswasser@paulweiss.com
ppatel@paulweiss.com

TDW

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Trials@uspto.gov
571-272-7822

Paper No. 15
Date: June 2, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORMYCON AG,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2025-00233
Patent 11,084,865 B2

Before SUSAN L. C. MITCHELL, MICHAEL A. VALEK, and JAMIE T. WISZ, *Administrative Patent Judges.*

VALEK, *Administrative Patent Judge.*

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Formycon Ag ("Petitioner") filed a Petition (Paper 2, "Pet."), seeking *inter partes* review of claims 1–12, 14–17, 19, 20, 22–36, 39–42, 44, 45, and 47–55 of U.S. Patent No. 11,084,865 B2 (Ex. 1001, "the '865 patent"). According to Petitioner, the Petition is a "copycat" of the one filed in IPR2024-00176, and Petitioner has filed a motion for joinder to that proceeding. (Paper 1, "Joinder Motion"). Regeneron Pharmaceuticals, Inc. ("Patent Owner") filed a Preliminary Response. Paper 10 ("Prelim. Resp.").

In its Preliminary Response, Patent Owner asks that we exercise discretion to deny institution under 35 U.S.C. § 314(a) in view of parallel district court litigation involving the '865 patent. *See* Prelim. Resp. 6–17. With our authorization, Petitioner filed a reply to Patent Owner's arguments for discretionary denial under § 314(a) (Paper 12 ("Reply")) and Patent Owner filed a sur-reply (Paper 13 ("Sur-reply")).

For the reasons set forth below, we exercise discretion under 35 U.S.C. § 314(a) to deny institution of the Petition and deny the Joinder Motion.

II. BACKGROUND

A. Real Parties in Interest

Petitioner and Patent Owner identify themselves as the only real parties in interest. Pet. 6; Paper 5, 1.

B. Related Matters

The '865 patent is currently asserted against Petitioner in *Regeneron Pharmaceuticals, Inc. v. Formycon AG*, No. 1:23-cv-97 (N.D.W. Va.).

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Pet. 6–7. The '865 patent has been asserted against a number of other defendants in the following matters: *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, No. 1:22-cv-61 (N.D.W. Va.) ("the Mylan case"); *Samsung Bioepis Co., Ltd.*, No. 1:23-cv-106 (N.D.W. Va.); *Regeneron Pharmaceuticals, Inc. v. Samsung Bioepis Co., Ltd.*, No. 1:23-cv-94 (N.D.W. Va.); *Regeneron Pharmaceuticals, Inc. v. Celltrion, Inc.*, Nos. 1:23-cv-89, 1:24-cv-53 (N.D.W. Va.); *Regeneron Pharmaceuticals, Inc. v. Amgen Inc.*, No. 2:24-cv-264 (C.D. Cal.); *Regeneron Pharmaceuticals, Inc. v. Sandoz Inc.*, No. 3:24-cv-876 (D.N.J.). Paper 5, 1–4. According to Patent Owner, "[t]he U.S. Judicial Panel on Multidistrict Litigation instituted a multidistrict litigation incorporating the aforementioned actions in the Northern District of West Virginia." *Id.* at 2. We refer to these cases collectively as "the MDL proceeding" and the case against Petitioner specifically as "the Formycon case."

The first of these cases, the Mylan case, has already proceeded through trial. Following a 9-day bench trial, the district court issued a detailed opinion finding that Mylan[1] infringed claims 4, 7, 9, 11, and 14–17 of the '865 patent and had not shown that those claims are invalid under 35 U.S.C. §§ 102, 103, or 112. Ex. 2001 ("Mylan Decision"), 3, 311–312. The district court's judgment was appealed and later the appeal was dismissed by joint stipulation as part of agreement between Mylan and Patent Owner resolving their disputes. *See* Ex. 1138, 1–2 (April 22, 2025 order entering joint stipulation and order offered by Patent Owner and Mylan).

[1] Mylan Pharmaceuticals Inc. and Biocon Biologics Inc. are joint defendants in this case. *See* Ex. 2001, 1. Here, we refer to them collectively as "Mylan."

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The district court has also conducted preliminary injunction ("PI") proceedings and granted PIs based on the '865 patent against Petitioner and two other biosimilar applicant defendants in the MDL proceeding. Ex. 2003 (order granting motion for preliminary injunction against Formycon) ("Formycon PI order"); *see also* Ex. 2002 (order granting motion for preliminary injunction against Samsung Bioepis ("SB")) ("SB PI order"); Ex. 2004 (order granting motion for preliminary injunction against Celltrion) ("Celltrion PI order"). Each of those decisions was appealed and recently affirmed by the Federal Circuit. *See* Ex. 2005–2007. The district court also considered and denied Patent Owner's motion for a preliminary injunction against Amgen. Paper 6, 3. According to Patent Owner, the Amgen PI motion was denied because the district court found it "was not likely to succeed on infringement." *Id.*

The '865 patent is also the subject of petitions for *inter partes* review filed by other defendants in the MDL proceeding, i.e., IPR2025-00176 (filed by SB) and IPR2025-00456 ("the Celltrion IPR"). The Celltrion IPR involves different grounds of unpatentability than those asserted here. *Compare* IPR2025-00456, Paper 2, 21 *with* Pet. 10 (identifying different grounds of unpatentability).

In addition, the parties identify IPR2021-00402, IPR2023-01312, and IPR2023-00462 as matters involving U.S. Patent No. 10,464,992 B2, which is related to the '865 patent. Pet. 7; Paper 5, 4–5; *see also* Ex. 1001, code (60).

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C. The '865 Patent

The '865 patent issued on August 10, 2021, and claims priority to a series of applications, the earliest of which was filed on June 16, 2006. Ex. 1001, codes (45), (60).

The '865 patent relates to "pharmaceutical formulations suitable for intravitreal administration comprising agents capable of inhibiting vascular endothelial growth factor (VEGF), and to methods for making and using such formulations." Ex. 1001, 1:45–49. According to the Specification, "[a] VEGF antagonist is a compound capable of blocking or inhibiting the biological action of vascular endothelial growth factor (VEGF), and includes fusion proteins capable of trapping VEGF." *Id.* at 6:27–30. Relevant to the claims challenged here, "the fusion protein comprises amino acids 27-457 of SEQ ID NO:4." *Id.* at 6:34–37. The parties refer to the fusion protein comprising this amino acid sequence as aflibercept. *See, e.g.*, Pet. 38; Prelim. Resp. 28, 32, 39 (referring to the "aflibercept amino acid sequence"). According to the Specification, in "a specific embodiment" this protein is "glycosylated at Asn residues 62, 94, 149, 222 and 308." Ex. 1001, 6:35–37.[2]

The '865 patent describes a "stable liquid ophthalmic formulation" comprising aflibercept, one or more organic co-solvents, e.g., polysorbate, one or more tonicity agents, e.g., sodium or potassium chloride, a buffering agent, e.g., phosphate buffer, and a stabilizing agent, e.g., sucrose, in varying

[2] According to Petitioner's declarant, "glycosylation refers to the process by which 'glycans' are created, altered, and attached to proteins," and because the '865 patent describes glycosylation at asparagine residues it is referring to "N-linked glycosylation," i.e., "glycans attached to the side-chain nitrogen atoms of asparagine residues." Ex. 1007 ¶¶ 26–27.

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amounts. *See id.* at 2:33–4:6. Such formulations may be "provided in a pre-filled syringe or vial, particularly suitable for intravitreal administration." *Id.* at 5:23–25.

D. Challenged Claims

The Petition challenges claims 1–12, 14–17, 19, 20, 22–36, 39–42, 44, 45, and 47–55. Pet. 9. Of these, claims 1, 26, and 51 are independent. Claim 1 is illustrative and reads as follows:

> 1. A vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises:
> a vascular endothelial growth factor (VEGF) antagonist
> an organic co-solvent,
> a buffer, and
> a stabilizing agent,
> wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4; 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.

Ex. 1001, 19:29–40. Claim 26 is nearly identical to claim 1, but recites the formulation in a "pre-filled syringe" instead of a vial. *Id.* at 20:66–21:12. Claims 2 and 27 depend from claims 1 and 26 respectively and further recite that the concentration of VEGF antagonist fusion protein is "40 mg/ml" and that the co-solvent comprises polysorbate. *Id.* at 19:41–43, 21:13–16. Claim 51 recites a similar ophthalmic formulation with the same limitations requiring, *inter alia*, that the VEGF antagonist fusion protein be glycosylated and have a 40 mg/ml concentration. *Id.* at 22:19–31.

E. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claim(s) Challenged	35 U.S.C. §[3]	Reference(s)/Basis
1–12, 14–17, 19, 20, 22–25, 51–53, 55	103(a)	Fraser,[4] Wulff,[5] 2006 Presentations,[6] '319 Publication,[7] FDA Guidance[8]
26–36, 39–42, 44, 45, 47–50, 54	103(a)	Fraser, Wulff, 2006 Presentations,'319 Publication, Nayar[9]

[3] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), included revisions to 35 U.S.C. § 103 that became effective after the filing of the applications to which the '865 patent claims priority. Therefore, we apply the pre-AIA version of 35 U.S.C. § 103.

[4] Fraser et al., "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function," 90(2) J. Clin. Endocrinol. Metab. 1114–22 (2005) (Ex. 1009) ("Fraser").

[5] Wulff et al., "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2," 143(7) Endocrinology 2797–807 (2002) (Ex. 1016) ("Wulff").

[6] The Petition refers to the three presentations in Exhibits 1011–1013, which were apparently obtained from the Internet Archive's Wayback Machine, as the "2006 Presentations." *See* Pet. 26–27.

[7] WO 00/75319 A1, published December 14, 2000 (Ex. 1029) ("'319 Publication").

[8] U.S. Dept. of Health and Human Serv., "Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics" (May 1999) (Ex. 1038) ("FDA Guidance").

[9] Nayar et al., *High Throughput Formulation: Strategies for Rapid Development of Stable Protein Products*, *in* RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS: THEORY AND PRACTICE (John F. Carpenter & Mark C. Manning 1st eds.) (2002) (Ex. 1020) ("Nayar").

Petitioner further relies on the declarations of Dr. Laird Forrest (Ex. 1002), Dr. Todd Lefkowitz (Ex. 1005), and Dr. Zhaohui Sunny Zhou (Ex. 1007) submitted with the Petition.

III. DISCRETION UNDER 35 U.S.C. § 314(A)

We begin by addressing Patent Owner's arguments for discretionary denial. As explained below, we find those arguments persuasive. Thus, we exercise discretion to deny institution of the Petition under 35 U.S.C. § 314(a) without reaching the merits of Petitioner's asserted grounds of unpatentability.

A. The Parties' Arguments

Patent Owner argues that we should exercise discretion under 35 U.S.C. § 314(a) to deny institution of *inter partes* review in view of the Mylan case and related MDL proceeding. Prelim. Resp. 6–17. In particular, Patent Owner argues the Petition was filed 365 days after Petitioner was sued and "implicates the same or substantially similar claims, prior-art references, and issues that have been decided repeatedly by the district court and the Federal Circuit" in "seven court decisions."[10] *Id.* at 6–7. According to Patent Owner, these decisions contain "hundreds of pages" on obviousness and obviousness-type double patenting ("ODP") addressing disputes that overlap with disputed issues in the Petition, and that "[g]iven

[10] The seven decisions Patent Owner refers to are the district court's bench trial opinion in the Mylan case (Ex. 2001), the district court's three orders granting Patent Owner's motions for preliminary injunction against Petitioner, Formycon, and Celltrion (Ex. 2002–2004), and the Federal Circuit's three decisions affirming those preliminary injunction orders (Ex. 2005–2007). *See* Prelim. Resp. 1.

the considerable investment of the parties and the courts in these proceedings, institution would be highly inefficient." *Id.* For these and other reasons, Patent Owner urges that the *Fintiv*[11] factors favor the exercise of discretion to deny institution under § 314(a). *Id.* at 6–17.

Petitioner disputes Patent Owner's assessment of the *Fintiv* factors and contends these factors do not favor the exercise of discretion to deny institution. *See generally* Reply. As an initial matter, Petitioner offers a *Sotera*[12] stipulation (Pet. 69–70), urging that it "obviates any overlap with the district court and ensures that this IPR will be a 'true alternative' to the [MDL proceeding]." Reply 3 (citing *Motorola Solutions, Inc. v. Stellar, LLC,* IPR2024-01205, Paper 19, 3–4 (PTAB Mar. 28, 2005)). Petitioner further points out that no trial date has been set in the MDL proceeding and that based on median time-to-trial data "trial would not be expected until September 2026 at the earliest—three months after an expected [Final Written Decision]." *Id.* at 3–4 (citing Ex. 1123; Ex. 1124).

Regarding the issue of the investment in the parallel proceeding, Petitioner argues that Patent Owner's reliance on the Mylan case is misplaced because that case is not ongoing and did not involve Petitioner. Reply 5–6. According to Petitioner, "the only ongoing proceeding involving Petitioner is the" MDL proceeding and there has been no substantial investment there "beyond the PI phase." *Id.* Even there, Petitioner contends there was no investment of "substantial resources ***related to the arguments***

[11] *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential) ("*Fintiv*").
[12] *Sotera Wireless, Inc. v. Masimo Corp.*, IPR2020-01019, Paper 12 (PTAB Dec. 1, 2020) (precedential as to § II.A.) ("*Sotera*").

raised in the Petition" because the PI proceedings involved only ODP and written description defenses. *Id.* at 7–8. Finally, Petitioner argues the merits of its Petition favor institution. *Id.* at 9–10.

Patent Owner responds, reiterating its position that the disputed issues in this proceeding are the same or substantially similar to issues that the district court and Federal Circuit have already addressed and resolved in its favor. *See* Sur-reply 1–3, 5–7. Patent Owner further contends that Petitioner's *Sotera* stipulation "does not remedy [the] substantial overlap—*e.g.*, motivation, reasonable expectation of success, and objective evidence––with its ODP arguments, which [Petitioner] remains free to advance." *Id.* at 8–9. Patent Owner also argues that "even were trial not to occur until September 2026, the investment in the parallel proceedings strongly favors discretionary denial." *Id.* at 9.

B. The Fintiv Factors and Related Guidance

The Board's precedential decision in *Fintiv* outlines factors that balance considerations of system efficiency, fairness, and patent quality when a patent owner raises an argument for discretionary denial due to the advanced state of a parallel proceeding, such as the MDL proceeding here. *Fintiv* 5–6. These factors are:

> 1. whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
>
> 2. proximity of the court's trial date to the Board's projected statutory deadline for a final written decision;
>
> 3. investment in the parallel proceeding by the court and the parties;

> 4. overlap between issues raised in the petition and in the parallel proceeding;
>
> 5. whether the petitioner and the defendant in the parallel proceeding are the same party; and
>
> 6. other circumstances that impact the Board's exercise of discretion, including the merits.

Id. "[I]n evaluating the factors, the Board takes a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review." *Id.* at 6.

The Office recently rescinded an earlier memorandum titled "Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation," and offered new guidance regarding the *Fintiv* analysis.[13] This guidance states that the recission "restore[s] policy in this area to the guidance in place before the Interim Procedure," including by making clear that a *Sotera* "stipulation (*i.e.*, a stipulation from a petitioner that, if an IPR or PGR is instituted, the petitioner will not pursue in district court . . . any ground raised or that could have been reasonably raised in the IPR/PGR) is highly relevant, but will not be dispositive by itself" and that "compelling merits alone is not dispositive." Guidance Memo. 1–3.

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[13] Memorandum from the Chief Administrative Patent Judge, *Guidance on USPTO's recission of "Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation* (March 24, 2025), available at https://www.uspto.gov/sites/default/files/documents/guidance_memo_on_interim_procedure_recission_20250324.pdf ("Guidance Memo"), 1.

C. Analysis

We now consider these factors to assess whether to exercise discretion to deny institution under 35 U.S.C. § 314(a) in this case.

i. Factor 1: likelihood of a stay in the MDL proceeding

No stay has been granted and neither party has asked for one. Prelim. Resp. 15; Reply 9. Accordingly, this factor is neutral.

ii. Factor 2: proximity of the trial date to the final written decision deadline

The projected statutory deadline for a final written decision ("FWD") in this case is one year after the entry of this decision, i.e., in June 2026.

We understand a trial date has not yet been set for the Formycon case or any of the other pending cases in the MDL proceeding. *See* Sur-reply 9 (acknowledging the lack of a scheduled trial date). According to Petitioner, there is no schedule in place following the PI proceedings and "the district court has not responded to the four status conference requests made by the *MDL* parties over the past seven months." Reply 4.

Patent Owner suggests the delay in entering a schedule following issuance of court's PI orders was to allow time for the appeals of those decisions and for the Mylan Decision to be resolved. *See* Prelim. Resp. 16 (explaining that while one defendant sought an earlier trial date, Patent Owner "proposed that the district court convene a status conference upon resolution of the remaining pending appeals and then determine an appropriate schedule"). "Given the conclusion of the appeals," the parties in the MDL proceeding have now jointly requested "an in-person status conference" with the district court "to set a case schedule for further proceedings." Ex. 2035, 1 (email on behalf of all parties to the MDL

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proceeding dated April 30, 2025). Thus, the parties in the MDL proceeding appear to be working toward entry of a trial schedule.

Nevertheless, at present, there is no set trial date and outside of the now-completed PI proceedings, no schedule has been set in the MDL proceeding. This suggests that the trial in the Formycon case may occur after the projected statutory deadline of June 2026. For this reason, factor 2 weighs against discretionary denial.

That said, we do not credit Petitioner's argument that trial "would not be expected until September 2026 at the earliest." Reply 4. Petitioner calculates this date based on statistics showing that the district court has a median time-to-trial of 627 days. Ex. 1123, 1. This median is presumably measured from the time the case was filed. Here, the Formycon case was filed in November 2023 and served in October 2024. Ex. 1116. But Petitioner inexplicably uses the time of its Reply (April 2025) as the starting point for its calculation "discounting [the district court's] median 3 months for the PI proceedings" to arrive at an expected September 2026 trial date. Reply 4. That calculation does not make sense. There are also a number of factors that distinguish the MDL proceeding from the average case,[14] which suggests that a prediction based on median time-to-trial statistics is unlikely to be accurate.

iii. Factor 3: investment in the parallel proceeding

Patent Owner asserts that the district court's consideration and grant of the PI against Petitioner alone constitutes a substantial investment, but that the district court did even more by conducting "a two-week trial in the

[14] For example, the MDL proceeding involves a number of defendants and patents, PIs, and extensive prior decisions involving the '865 patent.

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Mylan case and three other preliminary-injunction proceedings focused on validity of the '865 patent." Prelim. Resp. 8. We agree.

Just within the context of the PI proceeding involving Petitioner, the district court considered testimony from eight different witnesses. *See* Formycon PI Order 13 (identifying witnesses).[15] It issued a thorough 203-page decision with voluminous citations to the record evidence, including more than 50 pages addressing Petitioner's ODP defense. *Id.* at 69–129. As explained in more detail below, that ODP defense presents a number of disputed issues that are the same or substantially similar to the disputed issues in this proceeding. On the preliminary record, the district court resolved those issues in Patent Owner's favor, finding that Petitioner had not raised a substantial question of validity. *Id.* at 71. The Federal Circuit affirmed that decision. Ex. 2006. The effort taken to litigate and decide the myriad issues raised by Patent Owner and Petitioner's PI filings demonstrates a substantial investment by the district court and the parties.

But this is far from the only substantial investment the district court has made. The district court completed claim construction proceedings and a full trial on the '865 patent in the Mylan case, issuing a more than 300-page trial decision.[16] That decision includes analysis of obviousness defenses

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[15] The parties waived an evidentiary hearing, so the PI motion was decided on written submissions. Formycon PI Order 12–13. Direct testimony was submitted in the form of declarations and both sides conducted cross-examination by deposition, which the district court also considered. *Id.* at 13; *see*, *e.g.*, *id.* at 88, 103, 105–106, 108, 110, 112, 114 (citing transcripts).

[16] Petitioner suggests the investment in the Mylan case is not relevant because the case is not ongoing and Petitioner was not a party to it. *See* Reply 5–6. We disagree. Indeed, *Fintiv* directly addresses this issue,

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based on one of the references (Fraser) in Petitioner's grounds and extensive fact-finding regarding Fraser and other references (e.g., Ex. 1029; Ex. 1039) that both sides rely on to support their positions in this proceeding. *See* Mylan Dec. 170–202. Moreover, the district court analyzed and credited the same objective indicia arguments Patent Owner raises here. *Id.* at 194–202; *see* Prelim. Resp. 60–63 (discussing objective indicia of non-obviousness).

In addition, the district court has decided PI motions based on the '865 patent for three other biosimilar applicants in the MDL proceeding. *See* Paper 5, 3. Similar to the Formycon PI Order, the district court's decisions granting preliminary injunctions against SB and Celltrion involve lengthy analysis of an ODP defense that overlaps with several of the disputed issues here. *See* SB PI Order 54–110; Celltrion PI Order 61–118 (analyzing ODP). These decisions were likewise affirmed by the Federal Circuit. Ex. 2005; Ex. 2007. All told, the district court's substantive decisions to date total almost a thousand pages, much of it directed to issues relating to claim construction and the validity of the '865 patent claims.

There is also the issue of Petitioner's delay in filing the Petition. The Petition was filed on November 29, 2024, a year after the filing of the Formycon case in the district court. Petitioner points out that the complaint in the Formycon case was not formally served until October 16, 2024. Reply

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explaining that "[e]ven when a petitioner is unrelated to a defendant . . . if the issues are the same as, or substantially similar to, those already . . . litigated . . . the Board may . . . exercise the authority to deny institution." *Fintiv* 14. Petitioner also points out that the permanent injunction against Mylan was vacated and all claims dismissed with prejudice pursuant to the parties' settlement of that case. *See* Reply 6 n. 5. But the Mylan Decision was not vacated (*see* Ex. 1138, 2) and even if it had been, this would not diminish the district court's extensive investment in the same.

2 (citing Ex. 1116). According to Petitioner, it is the date of service, not filing, that matters because "35 U.S.C. § 315(b) considers only the date that a petitioner was properly served." *Id.* (citing *GoPro, Inc. v. 360Heros, Inc.*, IPR2018-01754, Paper 38, 9 (PTAB Aug. 23, 2019) (precedential)). We disagree because Petitioner's argument confuses the date for calculating a time bar under section 315(b) with the concern over undue delay in filing a petition to challenge a patent asserted in a parallel proceeding. Here, it is beyond dispute that Petitioner was aware of and actively litigating the Formycon case soon after it was filed. *See* Formycon PI Order 9–13 (describing district court proceedings, including a scheduling conference on January 5, 2024). Accordingly, the fact that Formycon was not formally served until October 2024 does not explain why Petitioner waited a year after it was sued to initiate this separate proceeding challenging the '865 patent. *See Fintiv* 11–12 (explaining that if "petitioner did not file the petition expeditiously" or "cannot explain the delay. . . these facts have favored denial").

Petitioner argues at the time the complaint was filed, it "could not know which patents [Patent Owner] would ultimately move forward on from . . . [the] group of ***thirty-nine*** asserted patents" in the complaint. Reply 5. However, Patent Owner's PI motion was filed on February 22, 2024 and asserts only four patents.[17] That motion also identifies a particular subset of the '865 patent's dependent claims Petitioner is accused of infringing. Formycon PI Order 10; *see also Fintiv* 11 ("[I]t is often reasonable for a

[17] Patent Owner later withdrew its motion with respect to three of those patents, limiting it to just the '865 patent. *See* Formycon PI Order 11 (stating Patent Owner did this to "streamline the issues in dispute").

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petitioner to wait to file its petition until it learns which claims are being asserted against it."). Thus, Petitioner was aware of the particular claims being asserted against it as early as February 2024 and could have filed a Petition challenging them far earlier than it did. Petitioner's delay in doing so is another fact in favor of denial. *See Fintiv* 11–12.

For these reasons, factor 3 weighs heavily in favor of discretionary denial.

iv. Factor 4: overlap in issues

Patent Owner asserts that *Fintiv* factor four weighs in favor of discretionary denial because the issues in the Petition substantially overlap with the MDL proceeding. Prelim. Resp. 11–15 (citing Pet. 1, 18 n.1, 23–30, 33–66, 69–70). Specifically, Patent Owner contends that, like Petitioner here, the defendants in the MDL proceeding have asserted that: (1) one of ordinary skill would have "had motivation to use 40 mg/mL aflibercept in an ophthalmic formulation"; (2) "aflibercept is necessarily glycosylated;" (3) "98% native conformation is inherent in formulations with the ingredients, concentrations, and pH recited by the claims [and] that the POSA was motivated with a reasonable expectation of success to make formulations with 98% native conformation;" and (4) "no objective evidence supported nonobviousness." Prelim. Resp. 14.

We agree these arguments are the same or similar to the arguments in the Petition. *See* Pet. 49–51 (arguing one of ordinary skill would have been motivated to set the concentration at 40 mg/ml), 38–40 (arguing that even though the asserted references do "not expressly teach glycosylated aflibercept" Wulff and the '319 publication teach expression in Chinese

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Hamster Ovary ("CHO") cells, which a skilled artisan would have known would result in the glycosylated protein); 40–48 (arguing that the claimed 98% native conformation after two months is inherent and/or obvious); 62–63 (arguing there are no objective indicia of non-obviousness for lack of nexus).

We also agree with Patent Owner that the district court made a number of fact findings in the Formycon PI Order and Mylan Decision that bear on these arguments, even though the grounds in the Petition are based on different combinations of art. *See* Prelim. Resp. 14–15 (identifying specific findings). For example, in the Mylan case, the district court found that the prior art taught away from the claimed 40 mg/ml concentration. Mylan Dec. 172–179. It also found that "objective evidence strongly supports nonobviousness" and that Patent Owner had established a sufficient nexus between that evidence and the '865 patent claims. *Id.* at 194–202; *see also* Formycon PI Order 126–129 (similar). Moreover, in the PI proceeding, the district court found that "aflibercept is not necessarily glycosylated" even when produced in a CHO cell and that one of ordinary skill in the art would not be motivated to use the glycosylated form of the protein in an ophthalmic formulation. Formycon PI Order 94–106; *see also* Ex. 2006, 14–16 (rejecting Petitioner's arguments that "the district court clearly erred in finding no motivation to pursue glycosylated aflibercept").

Petitioner attempts to distinguish these and other findings from the district court by arguing that the present obviousness grounds differ from its ODP defense, which "requires comparison between ***claims***, not disclosures," and that the findings in the Mylan case "were made on a different record with different parties and a narrower set of claims." Reply 7–9. Those

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differences, however, appear to be relatively minor on the record before us. At most, they show that some of the disputed issues that have already been considered by the district court in its Mylan Decision and PI Orders, and that remain before it now in those cases still pending in the MDL proceeding, are substantially similar, as opposed to identical, to the disputed issues in the Petition. Either way, there is substantial overlap between the issues both previously litigated and currently pending before the district court and the grounds in the Petition.

The *Sotera* stipulation is an attempt to counterbalance the concerns raised by this overlap, but given the circumstances, it does not effectively mitigate them. First, the disputed issues for Petitioner's ODP defense are the same or substantially similar to those for the obviousness grounds in the Petition, but the *Sotera* stipulation does not prevent Petitioner from litigating those issues before both the district court (as part of its ODP defense) and here in the event an IPR is instituted.[18] Second, the MDL proceeding involves other biosimilar applicant defendants who are similarly motivated to try to invalidate the '865 patent claims, but are not subject to any *Sotera* stipulation. Even if we institute review on Petitioner's grounds here, those other defendants remain free to litigate the same grounds in the consolidated MDL proceeding. For these reasons and given the particular circumstances

[18] ODP or nonstatutory double patenting is, as the name implies, not premised on any statute. *See, e.g.*, *Ostuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1297 (Fed. Cir. 2012) ("Nonstatutory double patenting is a judicially created doctrine grounded in public policy."). Accordingly, it is *not* a ground Petitioner reasonably could have raised in this IPR. *See* 35 U.S.C. § 311(b) (inter partes review may be requested "only on a ground that could be raised under section 102 or 103").

of this case, Petitioner's *Sotera* stipulation does not sufficiently mitigate the risks of duplicated efforts or inconsistent decisions by making this IPR a "true alternative" to resolution of these issues by the district court. *See Motorola,* IPR2024-01205, Paper 19 at 3–4 (determining on Director Review that a *Sotera* stipulation did not ensure IPR would be a "true alternative" because Petitioner's invalidity arguments "include combinations of the prior art asserted in these proceedings with unpublished system prior art, which Petitioner's stipulation is not likely to moot" and thus the same or similar issues would remain in the parallel proceeding); *SAP America, Inc. v. Cyandia, Inc.*, IPR2024-01496, Paper 13, 8–9 (PTAB Apr. 7, 2025) (similar).

Finally, while the Petition challenges a broader set of claims than those asserted in the Formycon case, that difference does not materially affect the overlap. The claims challenged in the Petition collectively raise the same disputed and overlapping issues identified above. Accordingly, even if some of the findings from the district court's prior decisions are not pertinent to some of the claims challenged in the Petition (*see* Reply 8 (comparing the "substantially broader" scope of claim 1 to claim 4)), the same issues would still need to be addressed by both the district court *and* the Board in our analysis of Petitioner's challenges to the narrower claims.

For these reasons, factor 4 weighs in favor of discretionary denial.

v. Factor 5: same or different parties

Petitioner and Patent Owner are both parties to the MDL proceeding. Therefore, this factor weighs in favor of exercising discretion to deny the Petition.

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vi. Factor 6: other circumstances, including the merits

This factor accounts for other relevant circumstances, including whether "the merits of a ground raised in the petition seem particularly strong on the preliminary record," which favors institution. *Fintiv* 14–15. "By contrast, if the merits of the grounds raised in the petition are a closer call, then that fact has favored denying institution when other factors favoring denial are present." *Id.* at 15.

The merits in this case are in the latter category, particularly as they relate to the limitations requiring an "ophthalmic formulation" containing "glycosylated" aflibercept. *See, e.g.*, Ex. 1001, 19:29–37 (claim 1). Based on the record in the PI proceeding, the district court found that one of ordinary skill in the art would not have been motivated to use glycosylated aflibercept in an ophthalmic formulation for several reasons, including that the larger glycosylated form of the protein would reduce retinal penetration, undesirably increase systemic exposure, and increase the risk of inflammation. Formycon PI Order 99–106. Petitioner's challenges to those findings were rejected on appeal. *See* Ex. 2006, 14–16. Nevertheless, Petitioner ignores the substance of the district court's reasoning and the supporting evidence cited by Patent Owner in its Preliminary Response.

Instead, Petitioner asserts that the merits of its grounds favor institution because in IPR2023-00462, "the Board found a reasonable likelihood that claims substantially similar to claim 1 were unpatentable over Fraser and instituted trial." Reply 9–10 (citing Ex. 1127). This argument is unpersuasive for several reasons. First, even if we agreed the claims in the two cases were substantially similar, there was no finding in IPR2023-00462 suggesting that the merits of the grounds there seemed "particularly strong

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on the preliminary record" as opposed to merely meeting the threshold for institution. *See Fintiv* 14–15.

Second, the claims challenged in IPR2023-00462 are not similar to the presently challenged claims in at least one key regard, i.e., they do not recite a "glycosylated" VEGF antagonist fusion protein in an "ophthalmic formulation suitable for intravitreal administration," *Compare* Ex. 1127, 6–7 (claims 1 and 10) *with* Ex. 1001, 19:29–41, 20:66–21:12; 22:18–31 (claims 1, 26, and 51). Rather, the claims in IPR2023-00462 recite a formulation containing a VEGF antagonist fusion protein produced in a CHO cell. *Id.* This difference is significant because while Wulff teaches that its VEGF trap was produced in a CHO cell, Petitioner concedes that Fraser and Wulff do not disclose that protein in an ophthalmic formulation, urging instead that one of skill in the art would have been motivated to make changes to those references' intravenous formulation to convert it to an intravitreal one. *See* Pet. 30–35. But it appears to be undisputed that one of ordinary skill in the art would have understood that aflibercept could be produced in either a glycosylated or unglycosylated form. Formycon PI Order 95 ("As explained by experts on both sides, aflibercept . . . can be produced from different cells, only some of which result in glycosylation of aflibercept."); *see also* Ex. 1029 (teaching expression in systems other than CHO cells); Ex. 1039 ¶ 38 (teaching glycosylation may be eliminated by using mutant CHO cell lines). Accordingly, to demonstrate that the claimed ophthalmic formulation is obvious, Petitioner would need to articulate some reasoning to explain why one of ordinary skill in the art would choose to use the glycosylated version in such a formulation. The fact that Petitioner elected not to mention, much less attempt to address the substance of the district court's findings

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that such a motivation was lacking, suggests a weakness in this aspect of its asserted grounds.[19]

For these reasons, factor 6 weighs in favor of discretionary denial.

D. Weighing of Fintiv Factors

Considering the *Fintiv* factors as part of a holistic analysis of all of the relevant circumstances of this case, we are persuaded that the interests of the efficiency and integrity of the system are served by invoking our authority under 35 U.S.C. § 314(a) to deny institution of a potentially meritorious Petition. That is, while the lack of a trial date (factor 2) weighs against denial, that single factor is solidly outweighed by the sum of the others, particularly factors 3, 4, and 6, which reflect the substantial investment in, and particular circumstances of, the parallel proceedings before the district court.

IV. CONCLUSION

For the foregoing reasons, we exercise discretion under 35 U.S.C. § 314(a) to deny the Petition. Because *inter partes* review has not been instituted, the Joinder Motion is denied.

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[19] We also have concerns regarding Petitioner's decision not to address the district court's prior finding that the art taught away from a 40 mg/ml concentration (*see* Mylan Dec. 172–179) and what that may signal regarding the relative strength of its arguments regarding that limitation. That limitation, however, is recited in only a subset of the challenged claims.

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V. ORDER

Accordingly, it is:

ORDERED that the Petition is denied, and no *inter partes* review is instituted; and

ORDERED that the Joinder Motion is denied.

For PETITIONER:

Louise E. Fogel
Grace Kim
Kristi L. R. Sawert
fogel@fr.com
PTABInbound@fr.com
sawert@fr.com

For PATENT OWNER:

David I. Berl
Andrew V. Trask
Arthur J. Argall
WILLIAMS & CONNOLLY LLP
dberl@wc.com
atrask@wc.com
aargall@wc.com

Elizabeth S. Weiswasser
Priyata Y. Patel
PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP
eweiswasser@paulweiss.com
ppatel@paulweiss.com

TDW

Petitioner Fresenius Ex. 1004, 0049

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United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/739,559	01/10/2020	Eric FURFINE	REGN-024CON10

CONFIRMATION NO. 1153

POWER OF ATTORNEY NOTICE

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

OC00000137527627

Date Mailed: 03/08/2023

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 02/28/2023.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/sltorres/

Petitioner Fresenius Ex. 1004, 0050

UNITED STATES PATENT AND TRADEMARK OFFICE

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Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/739,559	01/10/2020	Eric FURFINE	REGN-024CON10

CONFIRMATION NO. 1153

191459
A&P - Regeneron (Prosecution)
601 Massachusetts Ave., NW
Washington, DC 20001-3743

POA ACCEPTANCE LETTER

OC00000137527635

Date Mailed: 03/08/2023

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 02/28/2023.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/sltorres/

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I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

[X] Practitioners associated with Customer Number: 191459

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

[X] The address associated with Customer Number: 191459

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee.

Signature /Frank R. Cottingham/	Date 13 January 2023
Name Frank R. Cottingham, Ph.D., J.D.	Telephone
Title Vice President, Associate General Counsel, Intellectual Property	

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 18 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Regeneron Pharmaceuticals, Inc.

Application No./Patent No.: 11,084,865 Filed/Issue Date: August 10, 2021

Titled: VEGF Antagonist Formulations Suitable for Intravitreal Administration

Regeneron Pharmaceuticals, Inc., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 053156, Frame 0704, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

   2. From: _____ To: _____

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The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Michael W. Lewis/	February 28, 2023
Signature	Date
Michael W. Lewis	76,829
Printed or Typed Name	Title or Registration Number

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The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/739,559	**02/28/2023 04:32:40 PM ET**	**REGN-024CON10**

Title of Invention

VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	11084865
CONFIRMATION #	1153	FILED BY	Kathi Moore
PATENT CENTER #	61664071	FILING DATE	01/10/2020
CUSTOMER #	96387	FIRST NAMED INVENTOR	Eric FURFINE
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Michael Lewis

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
P35063US12-373c.pdf	3	Assignee showing of ownership per 37 CFR 3.73	110 KB
POA-Regeneron.pdf	2	Power of Attorney	3810 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
P35063US12-373c.pdf	75C97560761AA430BA10878F56CAD405828351AA4CB6E5CC04730C21A1B55716B89686815429571CE9035CB2079FD3898DF7DA8DCEA051B45BF3C9A2FB9D8822

POA-Regeneron.pdf BDECE05D2F51BBCDB37E674E496644E6B6A6D74B020A14B4FE816D8015E1EC9283171078BA0A0E1076CA395ADB4C661BA9E9C16DA415BC049CBFF10B715A0675

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Northern District of West Virginia on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
1:22-cv-61	8/2/2022	Northern District of West Virginia

PLAINTIFF	DEFENDANT
REGENERON PHARMACEUTICALS, INC.	MYLAN PHARMACEUTICALS, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	See attached		
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
CHERYL DEAN RILEY	/s/ D. Kinsey	8/3/2022

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
7,070,959	July 4, 2006	Regeneron Pharmaceuticals, Inc.
9,222,106	December 29, 2015	Regeneron Pharmaceuticals, Inc.
9,254,338	February 9, 2016	Regeneron Pharmaceuticals, Inc.
9,669,069	June 6, 2017	Regeneron Pharmaceuticals, Inc.
9,816,110	November 14, 2017	Regeneron Pharmaceuticals, Inc.
10,130,681	November 20, 2018	Regeneron Pharmaceuticals, Inc.
10,406,226	September 10, 2019	Regeneron Pharmaceuticals, Inc.
10,415,055	September 17, 2019	Regeneron Pharmaceuticals, Inc.
10,464,992	November 5, 2019	Regeneron Pharmaceuticals, Inc.
10,669,594	June 2, 2020	Regeneron Pharmaceuticals, Inc.
10,857,205	December 8, 2020	Regeneron Pharmaceuticals, Inc.
10,888,601	January 12, 2021	Regeneron Pharmaceuticals, Inc.
10,927,342	February 23, 2021	Regeneron Pharmaceuticals, Inc.
10,973,879	April 13, 2021	Regeneron Pharmaceuticals, Inc.
11,053,280	July 6, 2021	Regeneron Pharmaceuticals, Inc.
11,066,458	July 20, 2021	Regeneron Pharmaceuticals, Inc.
11,084,865	August 10, 2021	Regeneron Pharmaceuticals, Inc.
11,104,715	August 31, 2021	Regeneron Pharmaceuticals, Inc.
11,174,283	November 16, 2021	Regeneron Pharmaceuticals, Inc.
11,186,625	November 30, 2021	Regeneron Pharmaceuticals, Inc.
11,253,572	February 22, 2022	Regeneron Pharmaceuticals, Inc.
11,299,532	April 12, 2022	Regeneron Pharmaceuticals, Inc.
11,306,135	April 19, 2022	Regeneron Pharmaceuticals, Inc.
11,332,771	May 17, 2022	Regeneron Pharmaceuticals, Inc.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/739,559	08/10/2021	11084865	REGN-024CON10	1153

96387 7590 07/21/2021

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Eric FURFINE, Concord, MA;
REGENERON PHARMACEUTICALS, INC., Tarrytown, NY;
Daniel DIX, LaGrangeville, NY;
Kenneth GRAHAM, Pleasant Valley, NY;
Kelly FRYE, Mendham, NJ;

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Receipt date: 03/02/2021

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/739,559
				Filing Date	2020-01-20
				First Named Inventor	Eric Furfine
				Art Unit	1647
				Examiner Name	Jon Lockard
Sheet	1	of	3	Attorney Docket Number	REGN-024CON10

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	6,171,586 B1	01/09/2001	Lam *et al.*	
	2	8,110,546 B2	02/07/2012	Dix *et al.*	
	3	10,464,992 B2	11/05/2019	Furfine *et al.*	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	2003/0113316 A1	06/19/2003	Kaisheva *et al.*	
	2	2003/0138417 A1	07/24/2003	Kaisheva *et al.*	
	3	2004/0197324 A1	10/07/2004	Liu *et al.*	
	4				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
Change(s) applied to document, /S.B./ 6/10/2021	1	~~WO~~ 97/04801 WO	02/13/1997	Genetech, Inc.		
	2					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	Petition for *Inter Partes* Review of U.S. Patent No. 10,464,992, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 59 pgs.	
	2	File History of U.S. Patent No. 10,464,992, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 124 pgs.	
	3	Declaration of Dr. Reiner Gentz, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 76 pgs.	
	4	Fraser *et al.*, "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function," *J. Clin. Endocrinol. & Metab.*, 90(2):1114-1122 (2004)	
	5	Wulff *et al.*, "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2," *Endocrinology*, 143(7):2797-2807 (2002)	
	6	Certificate of Correction dated March 3, 2020, in U.S. Patent No. 10,464,992, 1 pg.	
	7	Holash *et al.*, "VEGF-Trap: A VEGF blocker with potent antitumor effects," *PNAS*, 99(17):11393-11398 (2002)	
	8	Response to Office Action in U.S. Patent Application No. 12/835,065 filed November 22, 2011, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 4 pgs.	
	9	Declaration Pursuant to 37 C.F.R. § 1.131 of Daniel B. Dix, Kelly Frye, and Susan Kautz in Support of Response to Office Action in U.S. Patent Application No. 12/835,065 filed November 22, 2011, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 11 pgs.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.B./

Doc Code: MFEE.C.AD

Document Description: Maintenance Fee Address Change

PTO/SB/47-EFS

FEE ADDRESS INDICATION FORM

Application Number	16739559	Art Unit	1647
Filing Date	10-Jan-2020	Examiner Name	JON LOCKARD
First Name Inventor	Eric FURFINE	Attorney Doc. Number	REGN-024CON10

INSTRUCTIONS: In order for the fee address identified on this form to be effective, the issue fee must have been paid for the application listed on this form. Only an address represented by a customer number can be established as the fee address for maintenance fee purposes (hereafter, fee address). A fee address should be established when correspondence related to maintenance fees should be mailed to a different address than the correspondence address for the application. For more information on customer numbers, see the Manual of Patent Examining Procedure (MPEP) § 403.

Please recognize as the Fee Address under the provisions of 37 CFR 1.363 the address associated with:

Customer Number:	96387 Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY CA 94065 UNITED STATES 650 327 3400 docket@bozpat.com

Signature :

I certify, in accordance with 37 CFR 1.4(d)(4) that I am an attorney or agent registered to practice before the Patent and Trademark Office who has filed and has been granted power of attorney in this application.

Signature	/Karl Bozicevic/	**Date**	06-30-2021
Name	Karl Bozicevic	**Registration Number**	28807

Electronic Patent Application Fee Transmittal

Application Number:	16739559
Filing Date:	10-Jan-2020
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-024CON10

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPL ISSUE FEE	1501	1	1200	1200
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1200**

Electronic Acknowledgement Receipt

EFS ID:	43131149
Application Number:	16739559
International Application Number:	
Confirmation Number:	1153
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-024CON10
Receipt Date:	30-JUN-2021
Filing Date:	10-JAN-2020
Time Stamp:	12:07:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1200
RAM confirmation Number	E20216TC07393548
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	Web85b.pdf	46437 46e3d3185102e28063f5e5e96bf4aceef709904b	no	2
Warnings:					
Information:					
2	Maintenance Fee Address Change	web85feeaddress.pdf	33177 c7b434615b0ac559f5b8639d1c1202cda27c8eb4	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32302 d2aeade9032e8fe90415c4d8f69d3981f7afb852	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	111916		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Document Description: Issue Fee Payment (PTO-85B)

Issue Fee Transmittal Form

Application Number	Filing Date	First Named Inventor	Atty. Docket No.	Confirmation No.
16739559	10-Jan-2020	Eric FURFINE	REGN-024CON10	1153

TITLE OF INVENTION :

VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

Entity Status	Application Type	Art Unit	Class - Subclass	EXAMINER
Regular Undiscounted	Utility under 35 USC 111(a)	1647	069700	JON LOCKARD

Issue Fee Due	Publication Due	Total Fee(s) Due	Date Due	Prev. Paid Fee
$1200	$0	$1200	09-Sep-2021	$0

1.Change of Correspondence Address and/or Indication Of Fee Address (37 CFR 1.33 & 1.363)

Current Correspondence Address:	Current Indicated Fee Address :
96387 Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY CA 94065 UNITED STATES 650 327 3400 docket@bozpat.com	
☐ Change of correspondence address requested, system generated AIA/122-EFS form attached	☒ Fee Address indication requested, system generated SB/47-EFS form attached

2.Entity Status

Change in Entity Status

○ Applicant certifying micro entity status; system generated Micro Entity certification form attached. See 37 CFR 1.29.
Note: Absent a valid certification of micro entity status, issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment. If this box is checked, you will be prompted to choose a micro entity status on the gross income basis (37 CFR 1.29(a)) or the institution of higher education basis (37 CFR 1.29(d)), and make the applicable certification online.

○ Applicant asserting small entity status. See 37 CFR 1.27.
Note: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

◉ Applicant changing to regular undiscounted fee status.
Note: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

Petitioner Fresenius Ex. 1004, 0068

Doc Code: IFEE PTOL/85B-EFS

Document Description: Issue Fee Payment (PTO-85B)

3.The Following Fee(s) Are Submitted:

☒ Issue Fee

☐ I authorize USPTO to apply my previously paid issue fee to the current fees due

☐ Publication Fee

☐ The Director is hereby authorized to apply my previously paid issue fee to the current fee due and to charge deficient fees to Deposit Account Number _____

☐ Advance Order - # of copies _____

☒ If **in addition to** the payment of the issue fee amount submitted with this form, there are any discrepancies in any amount(s) due, the Director is authorized to charge any deficiency or credit any overpayment, to Deposit Account Number 500815 . The **issue fee must be submitted** with this form. **If payment of the issue fee does not accompany this form, checking this box and providing a deposit account number will NOT be effective to satisfy full payment of the fee(s) due.**

4.Firm and/or Attorney Names To Be Printed

NOTE: If no name is listed, no name will be printed
For printing on the patent front page, list to be displayed as entered

1. Karl Bozicevic
2. Bozicevic Field & Francis LLP
3.

5.Assignee Name(s) and Residence Data To Be Printed

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

Name	City	State	Country	Category
REGENERON PHARMACEUTICALS, INC.	Tarrytown	NEW YORK	united states	corporation

6.Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am an attorney or agent registered to practice before the Patent and Trademark Office who has filed and has been granted power of attorney in this application. I also certify that this Fee(s) Transmittal form is being transmitted to the USPTO via EFS-WEB on the date indicated below.

Signature	/Karl Bozicevic/	**Date**	06-30-2021
Name	Karl Bozicevic	**Registration Number**	28807

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/739,559	01/10/2020	Eric FURFINE	REGN-024CON10	1153

96387 7590 06/29/2021

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
LOCKARD, JON MCCLELLAND	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
06/29/2021	ELECTRONIC

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.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

Response to Rule 312 Communication	Application No.	Applicant(s)	
	16/739,559	FURFINE et al.	
	Examiner	Art Unit	AIA (FITF) Status
	JON M LOCKARD	1647	No

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

1. ☑ The amendment filed on 16 June 2021 under 37 CFR 1.312 has been considered, and has been:

a) ☐ entered.

b) ☑ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.

Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647

OK TO ENTER: /J.L/

06/22/2021

Electronically filed 6/16/2021		
AMENDMENT UNDER 37 C.F.R. §1.312	Attorney Docket No.	REGN-024CON10
	Confirmation No.	1153
	First Named Inventor	Eric Furfine
	Application Number	16/739,559
Address to:	Filing Date	January 10, 2020
Mail Stop ISSUE FEE	Group Art Unit	1647
Commissioner for Patents	Examiner Name	Jon McClelland Lockard
P.O. Box 1450	Title: "*VEGF Antagonist Formulations Suitable for Intravitreal Administration*"	
Alexandria, VA 22313-1450		

Sir:

This amendment is submitted further to the Notice of Allowance and Fees Due dated June 9, 2021. Applicants submit that the amendments set forth below raise no new issues and simply corrects informalities in the claims. Entry of these amendments is thus respectfully requested.

Electronically filed 6/16/2021		
AMENDMENT UNDER 37 C.F.R. §1.312	Attorney Docket No.	REGN-024CON10
	Confirmation No.	1153
	First Named Inventor	Eric Furfine
	Application Number	16/739,559
Address to:	Filing Date	January 10, 2020
Mail Stop ISSUE FEE	Group Art Unit	1647
Commissioner for Patents	Examiner Name	Jon McClelland Lockard
P.O. Box 1450	Title: "*VEGF Antagonist Formulations Suitable for Intravitreal Administration*"	
Alexandria, VA 22313-1450		

Sir:

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AMENDMENTS TO THE CLAIMS

1.-11. (Canceled)

12 (Previously Presented) A vial comprising:– an ophthalmic formulation suitable for intravitreal administration that comprises:

a vascular endothelial growth factor (VEGF) antagonist

an organic co-solvent,

a buffer, and

a stabilizing agent,

wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4; 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.

13.-20. (Cancelled).

21. (Previously Presented) The vial of claim 12, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate.

22. (Previously Presented) The vial of claim 21, wherein said organic co-solvent comprises 0.01% to 3% polysorbate.

23. (Previously Presented) The vial of claim 21, wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20.

24. (Previously Presented) The vial of claim 21, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.

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25. (Previously Presented) The vial of claim 23, wherein said buffer comprises a phosphate buffer.

26. (**Currently Amended**) The vial of claim 23, **wherein said buffer comprises 5-25 mM buffer** ~~**wherein said buffer comprises 5-25 mM buffer**~~.

27. (Previously Presented) The vial of claim 23, wherein said buffer comprises a pH between about 5.8-7.0.

28. (Previously Presented) The vial of claim 23, wherein said buffer comprises a pH about 6.2- 6.3.

29. (Previously Presented) The vial of claim 23, wherein said stabilizing agent comprises a sugar.

30. (Previously Presented) The vial of claim 29, wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.

31. (**Currently Amended**) The vial of claim 23, wherein said stabilizing agent comprises **1.0-10%** ~~**1.0- 10%**~~ of sucrose.

32. (**Currently Amended**) The vial of claim 23, wherein said stabilizing agent comprises **1.0-7.5%** ~~**1.0- 7.5%**~~ of sucrose.

33. (Previously Presented) The vial of claim 23, wherein said formulation further comprises a tonicity agent.

34. (Previously Presented) The vial of claim 23, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4.

35. (Previously Presented) The vial of claim 23, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5°C.

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36. (Previously Presented) The vial of claim 23, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5°C as measured by size exclusion chromatography.

37. (Previously Presented) The vial of claim 23, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C for 24 months as measured by size exclusion chromatography.

38. (Previously Presented) The vial of claim 23, wherein said formulation does not contain phosphate.

39. (**Currently Amended**) The ~~**glass**~~ vial of claim 23, wherein said formulation does not contain trehalose.

40. (Previously Presented) The vial of claim 31, wherein said formulation further comprises a tonicity agent.

41. (Previously Presented) The vial of claim 31, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4.

42. (Previously Presented) The vial of claim 31, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5°C.

43. (Previously Presented) The vial of claim 31, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5°C as measured by size exclusion chromatography.

44. (Previously Presented) The vial of claim 31, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5°C for 24 months as measured by

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size exclusion chromatography.

45. (Previously Presented) A pre-filled syringe comprising an ophthalmic formulation suitable for intravitreal administration comprising:
a vascular endothelial growth factor (VEGF) antagonist fusion protein,
an organic co-solvent,
a buffer, and
a stabilizing agent;
wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4; and
wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5°C for two months as measured by size exclusion chromatography.

46. (Previously Presented) The pre-filled syringe of claim 45, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate.

47. (Previously Presented) The pre-filled syringe of claim 46, wherein said organic co-solvent comprises 0.01% to 3% polysorbate.

48. (Previously Presented) The pre-filled syringe of claim 46, wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20.

49. (Previously Presented) The pre-filled syringe of claim 46, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.

50. (Previously Presented) The pre-filled syringe of claim 48, wherein said buffer comprises a phosphate buffer.

51. (Previously Presented) The pre-filled syringe of claim 48, wherein said buffer comprises 5-25 mM buffer.

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52. (Previously Presented) The pre-filled syringe of claim 48, wherein said buffer comprises a pH between about 5.8-7.0.

53. (Previously Presented) The pre-filled syringe of claim 48, wherein said buffer comprises a pH about 6.2-6.3.

54. (Previously Presented) The pre-filled syringe of claim 48, wherein said stabilizing agent comprises a sugar.

55. (Previously Presented) The pre-filled syringe of claim 54, wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.

56. (Previously Presented) The pre-filled syringe of claim 48, wherein said stabilizing agent comprises 1.0-10% of sucrose.

57. (Previously Presented) The pre-filled syringe of claim 48, wherein said stabilizing agent comprises 1.0-7.5% of sucrose.

58. (Previously Presented) The pre-filled syringe of claim 48, wherein said formulation further comprises a tonicity agent.

59. (Previously Presented) The pre-filled syringe of claim 48, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4.

60. (Previously Presented) The pre-filled syringe of claim 48, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5°C.

61. (Previously Presented) The pre-filled syringe of claim 48, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5°C as measured by

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size exclusion chromatography.

62. (Previously Presented) The pre-filled syringe of claim 48, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5°C for 24 months as measured by size exclusion chromatography.

63. (Previously Presented) The pre-filled syringe of claim 48, wherein said formulation does not contain phosphate.

64. (Previously Presented) The pre-filled syringe of claim 48, wherein said formulation does not contain trehalose.

65. (Previously Presented) The pre-filled syringe of claim 56, wherein said formulation further comprises a tonicity agent.

66. (Previously Presented) The pre-filled syringe of claim 56, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4.

67. (Previously Presented) The pre-filled syringe of claim 56, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5°C.

68. (Previously Presented) The pre-filled syringe of claim 56, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5°C as measured by size exclusion chromatography.

69. (Previously Presented) The pre-filled syringe of claim 56, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5°C for 24 months as measured by size exclusion chromatography.

70. (Previously Presented) An ophthalmic formulation comprising:

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(a) 40 mg/ml of a glycosylated VEGF antagonist fusion protein comprising amino acids 27-457 of SEQ ID NO:4;

(b) 0.03% to 0.1% polysorbate;

(c) 5-40 mM of sodium phosphate buffer, pH between 5.8-7.0; and

(d) sucrose;

wherein the ophthalmic formulation is suitable for intravitreal administration; and

wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5°C for 2 months as measured by size exclusion chromatography.

71. (Previously Presented) The formulation of claim 70, wherein said formulation comprises 10 mM sodium phosphate buffer, 0.03% polysorbate, 5% sucrose, and a pH between 6.2-6.3.

72. (Previously Presented) The formulation of claim 71, wherein said formulation further comprises 40 mM NaCl.

73. (Previously Presented) The formulation of claim 72, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4.

74. (Previously Presented) The formulation of claim 70, wherein said formulation comprises at least 5% sucrose.

75. (Previously Presented) The formulation of claim 70, wherein said formulation comprises 1-10% sucrose.

76. (Previously Presented) A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim 70.

77. (Previously Presented) A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim 71.

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78. (Previously Presented) A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim 72.

79. (Previously Presented) A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim 73.

80. (Previously Presented) A vial suitable for intravitreal administration comprising the formulation of claim 70.

81, (Previously Presented) A vial suitable for intravitreal administration comprising the formulation of claim 71.

82. (Previously Presented) A vial suitable for intravitreal administration comprising the formulation of claim 72.

83. (Previously Presented) A vial suitable for intravitreal administration comprising the formulation of claim 73.

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REMARKS

Formal Matters

Claims 12 and 21-83 are still pending and allowed after entry of the amendments set forth herein.

Claims 26, 31, 32 and 39 have been amended to correct informalities in the claims.

Claim 26 is rewritten to eliminate a line break which previously occurred just before the second occurrence of the word buffer. The amendment is formal in nature.

Claims 31 and 32 are amended and to make the spacing between the numbers and dashes the same as the spacing in other claims. The amendment is formal in nature.

Claim 39 is amended to delete the word "glass" and make the claim consistent with the terminology used in claims 38 – 44.

No new matter has been added.

CONCLUSION

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-024CON10.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: June 16, 2021 By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Petitioner Fresenius Ex. 1004, 0082

Electronic Acknowledgement Receipt

EFS ID:	43000320
Application Number:	16739559
International Application Number:	
Confirmation Number:	1153
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-024CON10
Receipt Date:	16-JUN-2021
Filing Date:	10-JAN-2020
Time Stamp:	12:01:07
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		REGN-024CON10_2021-06-15_Amend_312.pdf	57324 e5bc01211ea4c529c710db83cb238cb875a66261	yes	10

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment after Notice of Allowance (Rule 312)	1	1
	Claims	2	9
	Applicant Arguments/Remarks Made in an Amendment	10	10
Warnings:			
Information:			
	Total Files Size (in bytes):	57324	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

96387 7590 06/09/2021

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/09/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/739,559	01/10/2020	Eric FURFINE	REGN-024CON10	1153

TITLE OF INVENTION: VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	09/09/2021

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

Petitioner Fresenius Ex. 1004, 0085

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

96387 7590 06/09/2021

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/739,559	01/10/2020	Eric FURFINE	REGN-024CON10	1153

TITLE OF INVENTION: VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	09/09/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	435-069700

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Petitioner Fresenius Ex. 1004, 0086

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/739,559	01/10/2020	Eric FURFINE	REGN-024CON10	1153

96387 7590 06/09/2021

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 06/09/2021

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Petitioner Fresenius Ex. 1004, 0087

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Petitioner Fresenius Ex. 1004, 0088

Notice of Allowability	Application No. 16/739,559	Applicant(s) FURFINE et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status No

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the Amendment filed 05 May 2021.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647

Petitioner Fresenius Ex. 1004, 0089

Continuation of 3. The allowed claim(s) is/are: 12 and 21-83 (renumbered as claims 1-3,5,4,6-11,20,12-19,21-28,30,29,31-36,45,37-44,46-51,56,59,62,52-54,57,60,63,55,58,61 and 64, respectively)

Notice of Pre-AIA or AIA Status

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

DETAILED ACTION

Status of Application, Amendments, and/or Claims

2. The Amendment filed 05 May 2021 has been received and entered in full. Claims 13-20 have been cancelled, and claims 21-83 have been added. Newly presented claims 21-83 will be examined as they fit under the rubric of the elected invention. Therefore, claims 12 and 21-83 are pending and the subject of this Office Action.

Terminal Disclaimer

3. The terminal disclaimer filed on 05 May 2021 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of **U.S. Patent No. 8,092,803** has been reviewed and is accepted. The terminal disclaimer has been recorded.

Withdrawn Objections and/or Rejections

4. The rejection of claims 12-20 on the ground of nonstatutory obviousness-type double patenting as set forth at pp. 3-5 of the previous Office action (mailed 06 January 2021) is withdrawn in view of Applicant's cancellation of claims 13-20, and the submission of a terminal disclaimer (filed 05 May 2021).

Summary

5. Claims 12 and 21-83 are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama**, can be reached on **(571) 272-2911**. The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1647

/J.L/
Examiner, Art Unit 1647
June 3, 2021

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/739,559	FURFINE et al.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

CPC						
Symbol					**Type**	**Version**
C07K	/	14	/	71	F	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	9	/	19	I	2013-01-01
A61K	/	38	/	1793	I	2013-01-01
C07K	/	14	/	4705	I	2013-01-01
A61M	/	5	/	178	I	2013-01-01
C07K	/	14	/	47	I	2013-01-01
A61K	/	9	/	0019	I	2013-01-01
A61K	/	38	/	179	I	2013-01-01
A61K	/	47	/	26	I	2013-01-01
A61K	/	47	/	02	I	2013-01-01
A61K	/	47	/	10	I	2013-01-01
C07K	/	2319	/	30	A	2013-01-01
C07K	/	2319	/	00	A	2013-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

/JON M LOCKARD/ Examiner, Art Unit 1647	03 June 2021	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	64	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	05 June 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20210602

Petitioner Fresenius Ex. 1004, 0093

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/739,559	FURFINE et al.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	38	/	17
A61K	/	38	/	18
C07K	/	19	/	00
C07K	/	14	/	71

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

/JON M LOCKARD/ Examiner, Art Unit 1647	03 June 2021	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	64	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	05 June 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20210602

Petitioner Fresenius Ex. 1004, 0094

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/739,559	FURFINE et al.
	Examiner	**Art Unit**
	JON M LOCKARD	1647

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	12	10	29	18	38	28	47	45	56	46	65	52	74	64	83
2	21	11	30	19	39	30	48	37	57	47	66	53	75		
3	22	20	31	21	40	29	49	38	58	48	67	54	76		
5	23	12	32	22	41	31	50	39	59	49	68	57	77		
4	24	13	33	23	42	32	51	40	60	50	69	60	78		
6	25	14	34	24	43	33	52	41	61	51	70	63	79		
7	26	15	35	25	44	34	53	42	62	56	71	55	80		
8	27	16	36	26	45	35	54	43	63	59	72	58	81		
9	28	17	37	27	46	36	55	44	64	62	73	61	82		

/JON M LOCKARD/ Examiner, Art Unit 1647	03 June 2021	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	64	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647	05 June 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20210602

Petitioner Fresenius Ex. 1004, 0095

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/739,559	FURFINE et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/19/2021	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
STIC Search of SEQ ID NO:4. See search results in SCORE.	03/19/2021	JML
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/19/2021	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/19/2021	JML
PALM: Inventor search.	03/19/2021	JML
IPR2021-00402 Reviewed petition for Inter Partes Review of U.S. Patent No. 10,464,992.	03/19/2021	JML

Petitioner Fresenius Ex. 1004, 0096

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/739,559	FURFINE et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	STIC Search of SEQ ID NO:4. See search results in SCORE.	06/03/2021	JML
	EAST (USPAT): See attached search history.	06/03/2021	JML
	PALM: Inventor search.	06/03/2021	JML

Petitioner Fresenius Ex. 1004, 0097

EAST Search History

EAST Search History (Interference) /J.L./

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	75	vegfr1r2$ and formulation	USPAT	OR	ON	2021/06/03 11:43
L2	36	l1 and (ophthalmic or intravitreal)	USPAT	OR	ON	2021/06/03 11:43
L3	97	(vegf adj (trap or antagonist)) same ophthalmic	USPAT	OR	ON	2021/06/03 11:43
L4	22	l3 same formulation	USPAT	OR	ON	2021/06/03 11:44
L5	22	l4 and (ophthalmic or intravitreal)	USPAT	OR	ON	2021/06/03 11:44
L6	55	l2 or l4	USPAT	OR	ON	2021/06/03 11:44
L7	5	l6 and (ophthalmic adj formulation).clm.	USPAT	OR	ON	2021/06/03 11:45
L8	357	(furfine-e$ dix-d$ graham-k$ frye-k$).in.	USPAT	OR	ON	2021/06/03 11:45
L9	10	l6 and l8	USPAT	OR	ON	2021/06/03 11:46

6/3/2021 11:52:40 AM
C:\Users\jlockard\Documents\EAST\Workspaces\16739559.wsp

/J.L./

Inventor Information for 16/739559

Inventor Name	City	State/Country
FURFINE, ERIC	CONCORD	MASSACHUSETTS
DIX, DANIEL	LAGRANGEVILLE	NEW YORK
GRAHAM, KENNETH	PLEASANT VALLEY	NEW YORK
FRYE, KELLY	MENDHAM	NEW JERSEY

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | **Inventors** | Applicants | Address | Fees | Post Info | Pre Gra

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PCT / [ ] / [ ] Search **or PG PUBS #** [ ] Search
Attorney Docket # [ ] Search
Bar Code # [ ] Search

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Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
* 16/739,559 *	16/739,559	FURFINE et al.	
	Examiner	**Art Unit**	
	LOCKARD, JON MCCLELLAND	1647	

Document Code - DISQ	**Internal Document - DO NOT MAIL**

TERMINAL DISCLAIMER	☑ APPROVED	☐ DISAPPROVED
Date Filed: 05 May 2021	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

/PAMELA A YOUNG/

Technology Center: OPLC

Telephone: (571)272-3622

_____

PTO/AIA/26 (04-14)
Approved for use through 11/30/2020. OMB 0651-0031
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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) REGN-024CON10

In re Application of: Regeneron Pharmaceuticals, Inc.

Application No.: 16/739,559

Filed: January 10, 2020

For: VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

The applicant, Regeneron Pharmaceuticals, Inc., owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 8092803 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 28807

/Karl Bozicevic, Reg. No. 28,807/ — Signature
4 May 2021 — Date

Karl Bozicevic — Typed or printed name

Partner — Title
650-833-7735 — Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	16739559
Filing Date:	10-Jan-2020
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Filer:	Karl Bozicevic/Kimberly Zuehlke
Attorney Docket Number:	REGN-024CON10

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	44	100	4400
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	170	170
		Total in USD ($)		**4570**

Electronic Acknowledgement Receipt

EFS ID:	42646415
Application Number:	16739559
International Application Number:	
Confirmation Number:	1153
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-024CON10
Receipt Date:	05-MAY-2021
Filing Date:	10-JAN-2020
Time Stamp:	17:18:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$4570
RAM confirmation Number	E202155H18504255
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		5050-US12_OA_Amdt_2021-05-05_REGN-024CON10.pdf	90021 a62d2d50f0f562e1650bcb3d9f6d50f204430d8f	yes	14
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	9	
	Applicant Arguments/Remarks Made in an Amendment		10	14	
Warnings:					
Information:					
2	Terminal Disclaimer Filed	5050US12_terminal_disclaimer_2021-05-04.pdf	240603 3617d64241e905a2f46ad48a316bb29eb42a6610	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32528 56601475d6a2a027d80ab2f03fc4528bec81b83e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	363152		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

INTERVIEW SUMMARY and AMENDMENT Under 37 CFR § 1.111	Attorney Docket No.	REGN-024CON10
	Confirmation No.	1153
	First Named Inventor	Eric Furfine
	Application Number	16/739,559
	Filing Date	January 10, 2020
Address to: Mail Stop Amendment Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Group Art Unit	1647
	Examiner Name	Jon McClelland Lockard
	Title: "*VEGF Antagonist Formulations Suitable for Intravitreal Administration*"	

Sir:

This amendment is responsive to the Office Action dated March 24, 2021, for which a three-month period for response was given making this amendment timely filed on or before June 24, 2021.

In view of the remarks put forth below, reconsideration and allowance are respectfully requested.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 10 of this paper.

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REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 12 and 21-83 are pending after entry of the amendments set forth herein.

Claims 1-11 were previously canceled and claims 13-20 are canceled herein without prejudice.[1]

New claims 21-83 are added. Support for these claims can be found throughout the originally filed application.

Claims 12 is amended to recite a "vial comprising an ophthalmic formulation suitable for intravitreal administration" Support for the amended claims can be found throughout the originally filed application, such as, for example, at ¶¶[0002], [0037], and [0048].

Claim 12 is further amended to specify that the "VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4" Support for the amended claims can be found throughout the originally filed application, such as, for example, at ¶[0046].

No new matter has been added.

Interview Summary

Applicants appreciate the Examiner taking the time for a Phone Interview on May 5, 2021 with the undersigned attorney.

During the interview it was pointed out that all the pending claims are interconnected by being directed to the invention which comprises:

(a) an ophthalmic formulation;

(b) a VEGF antagonist active ingredient which is defined by amino acids 27-457 of SEQ ID NO 4, and

(c) defined by the limitation "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."

[1] As noted below, claims 12 to 20 correspond to the claims 1 to 9 submitted on January 10, 2020 which were inadvertently misnumbered.

Petitioner Fresenius Ex. 1004, 0109

It was pointed out that the newly added claims 45 through 69 correspond to claims that were pending within the group of claims 42 – 71 that were canceled by a Supplemental Amendment filed on April 26, 2021 in the related application serial number 16/582, 486. This specific information on a related application is provided solely for the convenience of the examiner who may have examined the claims canceled and the related application serial number 16/582, 486. Complete information relating to related applications as provided below in the McKesson Statement.

No agreement was reached in the interview and the undersigned indicated a response would be filed addressing the issues raised in the Office Action dated March 24, 2021.

Objections to the Specification

The Office objects to the specification requesting inclusion of the status of the parent nonprovisional applications in the first sentence of the specification. Applicant amends the specification accordingly.

Claim Objections

The Office objects to the pending claims under 37 C.F.R. 1.126 for failing to preserve the original claim numbering through the prosecution. The Office kindly addresses this issue by renumbering misnumbered claims 1-9 (as filed on January 10, 2020) as pending claims 12-20. Applicant maintains this numbering system in the present response. Applicant therefore respectfully submits that this objection is moot.

Obviousness Type Double Patenting Rejections

Claims 12-20 were rejected under the doctrine of obviousness-type double patenting over claims 1-7 and 11-17 of issued U.S. Patent 8,092,803.

Without acquiescing to the validity of the rejection and merely to expedite prosecution of the application Applicant submits an e-Terminal Disclaimer with respect to U.S. Patent 8,092,803 thereby rendering the rejection moot.

Claims 12-20 were rejected for obviousness type-double patenting over claims 1-15 and 17 of issued U.S. Patent 7,608,261.

The rejection is respectfully traversed as applied and as it might be applied to the

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presently pending claims. All the independent claims include an element relating to the stability of the protein conformation in storage over a period of time. This element is not contained within any of the claims of the '261 patent.

In view of distinguishing features between the claims as amended and the claims of the '261 patent the rejection should be reconsidered and withdrawn.

Claims 12-20 were rejected for obviousness-type double patenting over claims 1-12 of issued U.S. Patent 9,340,594.

The claims 1-12 of the '594 patent do not include elements relating to the percentage of the VEGF antagonist which maintains its conformation following storage over a given period of time. All the independent claims include an element relating to the stability of the protein conformation in storage over a period of time. In view of such the rejection should be reconsidered and withdrawn.

Claims 12-20 were rejected for obviousness-type double patenting over claims 1-12 of issued U.S. Patent 9,914,763. The rejection is traversed as applied and as it might be applied to the amended claims.

The claims of the '763 patent do not include elements relating to the stability of the VEGF antagonist over time when stored which element is included in the claims of the present application by amendment. All the independent claims include an element relating to the stability of the protein conformation in storage over a period of time. In view of such the rejection should be reconsidered and withdrawn.

Statement under 37 C.F.R. §§1.56 and 1.2

Applicants hereby advise the Examiner of the status of a co-pending application in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 11/818,463, filed June 14, 2007 which issued as U.S. Patent No. 7,608,261 on October 27, 2009.

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Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 12/560,885, filed September 16, 2009 which issued as U.S. Patent No. 7,807,164 on October 5, 2010.

Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 12/833,417, filed July 9, 2010 which issued as U.S. Patent No. 8,092,803 on January 10, 2012.

Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 13/329,770, filed December 19, 2011 which issued as U.S. Patent No. 8,481,046 on July 9, 2013.

Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 13/914,996, filed June 11, 2013 which issued as U.S. Patent No. 8,802,107 on August 12, 2014.

Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 14/330,096, filed July 14, 2014 which issued as U.S. Patent No. 9,340,594 on May 17, 2016.

Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15/095,606, filed April 11, 2016 which issued as U.S. Patent No. 9,914,763 on March 13, 2018.

Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15/151,776, filed May 11, 2016 which issued as U.S. Patent No. 9,580,489 on February 28, 2017.

Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15/879,294, filed January 24, 2018 which issued as U.S. Patent No. 10,400,025 on September 3, 2019.

Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 16/159,269, filed October 12, 2018 which issued as U.S. Patent No. 10,464,992 on November 5, 2019.

Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 16/582,486, filed September 25, 2019 for which an Office Action was mailed January 6, 2021 and a response was filed on March 2, 2021.

Applicants wish to bring to the Examiner's attention U.S. Patent Reexamination Control No. 90/014,448 of U.S. Patent No. 10,464,992, filed February 11, 2020. A Petition Under 37 C.F.R. § 1.182 to Expedite a Concurrent Petition and Petition to Vacate Reexamination Order was filed May 29, 2020 and an Opposition to Petition was filed June 12, 2020.

Applicants wish to bring to the Examiner's attention Inter Partes Review Application No. IPR2021-00402 of U.S. Patent No. 10,464,992, filed on January 7, 2021.

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These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

CONCLUSION

Applicants submit that all the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-024CON10.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 5 May 2021

By: /Karl Bozicevic, Reg. No. 28,807 /
Karl Bozicevic, Reg. No. 28,807

Enclosure: Terminal Disclaimer to
U.S. Patent Nos. 8,092,803

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Direct: (650) 833-7735
Facsimile: (650) 327-3231

Petitioner Fresenius Ex. 1004, 0113

AMENDMENTS TO THE SPECIFICATION

[0001] This application is a continuation application of U.S. patent application Ser. No. 16/582,486, filed on Sep. 25, 2019, which is a continuation application of U.S. patent application Ser. No. 16/159,269, filed on Oct. 12, 2018, which issued as U.S. Pat. No. 10,464,992 on Nov. 5, 2019, which is a continuation application of U.S. patent application Ser. No. 15/879,294, which issued as U.S. Pat. No. 10,400,025 on Sep. 2, 2013, filed on Jan. 24, 2018, which is a continuation application of U.S. patent application Ser. No. 15/095,606, filed on April 11, 2016, which issued as U.S. Pat. No. 9,914,763 on Mar. 13, 2018, which is a continuation application of U.S. patent application Ser. No. 14/330,096, filed Jul. 14, 2014, which issued as U.S. Pat. No. 9,340,594 on May 17, 2016, which is a continuation of U.S. patent application Ser. No. 13/914,996, filed Jun. 11, 2013, which issued as U.S. Pat. No. 8,802,107 on Aug. 12, 2014, which is a continuation application of U.S. patent application Ser. No. 13/329,770, filed Dec. 19, 2011, which issued as U.S. Pat. No. 8,481,046 on Jul. 9, 2013, which is a continuation application of U.S. patent application Ser. No. 12/833,417, filed Jul. 9, 2010, which issued as U.S. Pat. No. 8,092,803 on Jan. 10, 2012, which is a continuation application of U.S. patent application Ser. No. 12/560,885, filed Sep. 16, 2009, which issued as U.S. Pat. No. 7,807,164 on Oct. 5, 2010, which is a divisional application of U.S. patent application Ser. No. 11/818,463, filed Jun. 14, 2007, which issued as U.S. Pat. No. 7,608,261 on Oct. 27, 2009, which claims the benefit under 35 U.S.C. .§119(e) of U.S. Provisional Application No. 60/814,484, filed June 16, 2006, which applications are each hereby incorporated by reference.

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AMENDMENTS TO THE CLAIMS

1.-11. (Canceled)

12 (Currently amended). A ~~pre-filled syringe~~ vial comprising~~:~~ an ophthalmic formulation suitable for intravitreal administration that comprises:

a vascular endothelial growth factor (VEGF) antagonist

an organic co-solvent,

a buffer, and

a stabilizing agent,

~~wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and~~

wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4; 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.

13.-20. (Cancelled).

21 (New). The vial of claim 12, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate.

22 (New). The vial of claim 21, wherein said organic co-solvent comprises 0.01% to 3% polysorbate.

23 (New). The vial of claim 21, wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20.

24 (New). The vial of claim 21, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.

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25 (New). The vial of claim 23, wherein said buffer comprises a phosphate buffer.

26 (New). The vial of claim 23, wherein said buffer comprises 5-25 mM buffer.

27 (New). The vial of claim 23, wherein said buffer comprises a pH between about 5.8-7.0.

28 (New). The vial of claim 23, wherein said buffer comprises a pH about 6.2- 6.3.

29 (New). The vial of claim 23, wherein said stabilizing agent comprises a sugar.

30 (New). The vial of claim 29, wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.

31 (New). The vial of claim 23, wherein said stabilizing agent comprises 1.0- 10% of sucrose.

32 (New). The vial of claim 23, wherein said stabilizing agent comprises 1.0- 7.5% of sucrose.

33 (New). The vial of claim 23, wherein said formulation further comprises a tonicity agent.

34 (New). The vial of claim 23, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4.

35 (New). The vial of claim 23, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5°C.

36 (New). The vial of claim 23, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5°C as measured by size exclusion chromatography.

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37 (New). The vial of claim 23, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C for 24 months as measured by size exclusion chromatography.

38 (New). The vial of claim 23, wherein said formulation does not contain phosphate.

39 (New). The glass vial of claim 23, wherein said formulation does not contain trehalose.

40 (New). The vial of claim 31, wherein said formulation further comprises a tonicity agent.

41 (New). The vial of claim 31, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4.

42 (New). The vial of claim 31, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5°C.

43 (New). The vial of claim 31, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5°C as measured by size exclusion chromatography.

44 (New). The vial of claim 31, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5°C for 24 months as measured by size exclusion chromatography.

45 (New). A pre-filled syringe comprising an ophthalmic formulation suitable for intravitreal administration comprising:
a vascular endothelial growth factor (VEGF) antagonist fusion protein,
an organic co-solvent,
a buffer, and

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a stabilizing agent;
wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4; and
wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5°C for two months as measured by size exclusion chromatography.

46 (New). The pre-filled syringe of claim 45, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate.

47 (New). The pre-filled syringe of claim 46, wherein said organic co-solvent comprises 0.01% to 3% polysorbate.

48 (New). The pre-filled syringe of claim 46, wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20.

49 (New). The pre-filled syringe of claim 46, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.

50 (New). The pre-filled syringe of claim 48, wherein said buffer comprises a phosphate buffer.

51 (New). The pre-filled syringe of claim 48, wherein said buffer comprises 5-25 mM buffer.

52 (New). The pre-filled syringe of claim 48, wherein said buffer comprises a pH between about 5.8-7.0.

53 (New). The pre-filled syringe of claim 48, wherein said buffer comprises a pH about 6.2-6.3.

54 (New). The pre-filled syringe of claim 48, wherein said stabilizing agent comprises a sugar.

55 (New). The pre-filled syringe of claim 54, wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.

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56 (New). The pre-filled syringe of claim 48, wherein said stabilizing agent comprises 1.0-10% of sucrose.

57 (New). The pre-filled syringe of claim 48, wherein said stabilizing agent comprises 1.0-7.5% of sucrose.

58 (New). The pre-filled syringe of claim 48, wherein said formulation further comprises a tonicity agent.

59 (New). The pre-filled syringe of claim 48, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4.

60 (New). The pre-filled syringe of claim 48, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5°C.

61 (New). The pre-filled syringe of claim 48, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5°C as measured by size exclusion chromatography.

62 (New). The pre-filled syringe of claim 48, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5°C for 24 months as measured by size exclusion chromatography.

63 (New). The pre-filled syringe of claim 48, wherein said formulation does not contain phosphate.

64 (New). The pre-filled syringe of claim 48, wherein said formulation does not contain trehalose.

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65 (New). The pre-filled syringe of claim 56, wherein said formulation further comprises a tonicity agent.

66 (New). The pre-filled syringe of claim 56, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4.

67 (New). The pre-filled syringe of claim 56, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5°C.

68 (New). The pre-filled syringe of claim 56, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5°C as measured by size exclusion chromatography.

69 (New). The pre-filled syringe of claim 56, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5°C for 24 months as measured by size exclusion chromatography.

70 (New). An ophthalmic formulation comprising:

(a) 40 mg/ml of a glycosylated VEGF antagonist fusion protein comprising amino acids 27-457 of SEQ ID NO:4;

(b) 0.03% to 0.1% polysorbate;

(c) 5-40 mM of sodium phosphate buffer, pH between 5.8-7.0; and

(d) sucrose;

wherein the ophthalmic formulation is suitable for intravitreal administration; and
wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5°C for 2 months as measured by size exclusion chromatography.

71 (New). The formulation of claim 70, wherein said formulation comprises 10 mM sodium phosphate buffer, 0.03% polysorbate, 5% sucrose, and a pH between 6.2-6.3.

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72 (New). The formulation of claim 71, wherein said formulation further comprises 40 mM NaCl.

73 (New). The formulation of claim 72, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4.

74 (New). The formulation of claim 70, wherein said formulation comprises at least 5% sucrose.

75 (New). The formulation of claim 70, wherein said formulation comprises 1-10% sucrose.

76 (New). A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim 70.

77 (New). A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim 71.

78 (New). A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim 72.

79 (New). A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim 73.

80 (New). A vial suitable for intravitreal administration comprising the formulation of claim 70.

81 (New). A vial suitable for intravitreal administration comprising the formulation of claim 71.

82 (New). A vial suitable for intravitreal administration comprising the formulation of claim 72.

83 (New). A vial suitable for intravitreal administration comprising the formulation of claim 73.

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PTO/SB/06 (09-11)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/739,559	Filing Date 01/10/2020	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	05/05/2021	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 64	Minus	** 20	= 44		x $100 =	4400
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	4400

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/ANGELA S WHITE/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/739,559	01/10/2020	Eric FURFINE	REGN-024CON10	1153

96387 7590 03/24/2021

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
03/24/2021	ELECTRONIC

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.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

Office Action Summary	Application No. 16/739,559	Applicant(s) FURFINE et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 10 January 2020.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 12-20 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 12-20 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☑ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

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

Status of Application, Amendments, and/or Claims

2. The preliminary amendment filed 10 January 2020 has been received and entered in full. Claims 1-10 are pending (renumbered as claims 12-20) and the subject of this Office Action.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 10 April 2020 and 02 March 2021 have been considered by the examiner.

4. The Third Party Submission under 37 CFR 1.290 has been considered by the Examiner.

Specification

5. The disclosure is objected to because of the following informalities: An updated status of the parent nonprovisional applications should be included in the first sentence of the specification.

Claim Objections

6. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 1-9 have been renumbered 12-20.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

8. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

9. The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

10. Claims 12-20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 and 11-17 of U.S. Patent No. 8,092,803. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the ophthalmic formulation of the VEGF antagonist recited in the instant claims is overlapping in scope with the ophthalmic formulation of VEGF antagonist recited in claims 1-7

and 11-17 of U.S. Patent No. 8,092,803. While the claims in '803 patent recite that the VEGF antagonist comprises amino acids 27-475 of SEQ ID NO:4, and not SEQ ID NO:4 as recited in the instant claims, it is noted that this species of VEGF antagonist is a specific preferred embodiment of VEGF antagonist (See column 5). Therefore, the claims are overlapping in scope.

11. Claims 12-20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 17 of U.S. Patent No. 7,608,261. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the ophthalmic formulation of the VEGF antagonist recited in the instant claims is overlapping in scope with the ophthalmic formulation of VEGF antagonist recited in claims 1-15 and 17 of U.S. Patent No. 7,608,261. Therefore, the claims are overlapping in scope.

12. Claims 12-20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 9,340,594. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the ophthalmic formulation of the VEGF antagonist recited in the instant claims is overlapping in scope with the ophthalmic formulation of VEGF antagonist recited in claims 1-11 of U.S. Patent No. 9,340,594. Therefore, the claims are overlapping in scope.

13. Claims 12-20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 9,914,763. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the ophthalmic formulation of the VEGF antagonist recited in the instant claims is overlapping in

scope with the ophthalmic formulation of VEGF antagonist recited in claims 1-11 of U.S. Patent No. 9,914,763. Therefore, the claims are overlapping in scope.

Summary

14. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama**, can be reached on **(571) 272-2911**. The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

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). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JON M LOCKARD/
Examiner, Art Unit 1647
March 19, 2021

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/739,559	FURFINE et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
NONE		03/19/2021	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
STIC Search of SEQ ID NO:4. See search results in SCORE.	03/19/2021	JML
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/19/2021	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/19/2021	JML
PALM: Inventor search.	03/19/2021	JML
IPR2021-00402 Reviewed petition for Inter Partes Review of U.S. Patent No. 10,464,992.	03/19/2021	JML

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

Petitioner Fresenius Ex. 1004, 0130

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/739,559	FURFINE et al.
	Examiner	Art Unit
	JON M LOCKARD	1647

Petitioner Fresenius Ex. 1004, 0131

Receipt date: 03/02/2021

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/739,559
				Filing Date	2020-01-20
				First Named Inventor	Eric Furfine
				Art Unit	1647
				Examiner Name	Jon Lockard
Sheet	1	of	3	Attorney Docket Number	REGN-024CON10

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	6,171,586 B1	01/09/2001	Lam *et al.*	
	2	8,110,546 B2	02/07/2012	Dix *et al.*	
	3	10,464,992 B2	11/05/2019	Furfine *et al.*	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	2003/0113316 A1	06/19/2003	Kaisheva *et al.*	
	2	2003/0138417 A1	07/24/2003	Kaisheva *et al.*	
	3	2004/0197324 A1	10/07/2004	Liu *et al.*	
	4				

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1	W0 97/04801	02/13/1997	Genetech, Inc.		
	2					

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	Petition for *Inter Partes* Review of U.S. Patent No. 10,464,992, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 59 pgs.	
	2	File History of U.S. Patent No. 10,464,992, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 124 pgs.	
	3	Declaration of Dr. Reiner Gentz, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 76 pgs.	
	4	Fraser *et al.*, "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function," *J. Clin. Endocrinol. & Metab.*, 90(2):1114-1122 (2004)	
	5	Wulff *et al.*, "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2," *Endocrinology*, 143(7):2797-2807 (2002)	
	6	Certificate of Correction dated March 3, 2020, in U.S. Patent No. 10,464,992, 1 pg.	
	7	Holash *et al.*, "VEGF-Trap: A VEGF blocker with potent antitumor effects," *PNAS*, 99(17):11393-11398 (2002)	
	8	Response to Office Action in U.S. Patent Application No. 12/835,065 filed November 22, 2011, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 4 pgs.	
	9	Declaration Pursuant to 37 C.F.R. § 1.131 of Daniel B. Dix, Kelly Frye, and Susan Kautz in Support of Response to Office Action in U.S. Patent Application No. 12/835,065 filed November 22, 2011, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 11 pgs.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/739,559
				Filing Date	2020-01-20
				First Named Inventor	Eric Furfine
				Art Unit	
				Examiner Name	
Sheet	2	of	3	Attorney Docket Number	REGN-024CON10

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	10	Resume of Reiner Gentz, Ph.D., as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 3 pgs.	
	11	Rudge *et al.*, "VEGF Trap as a Novel Antiangiogenic Treatment Currently in Clinical Trials for Cancer and Eye Diseases, and VelociGene®-based Discovery of the Next Generation of Angiogenesis Targets," *Cold Spring Harbor Symposia on Quantitative Biology*, 70:411-418 (2004)	
	12	Chi *et al.*, "Physical Stability of Proteins in Aqueous Solution: Mechanism and Driving Forces in Nonnative Protein Aggregation," *Pharmaceutical Research*, 20(9):1325-1336 (2003)	
	13	Bontempo, "Preformulation Development of Parenteral Biopharmaceuticals," *Drugs and the Pharmaceutical Sciences*, 85:91-108 (1997)	
	14	"Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products," U.S. Department of Health and Human Services, Food and Drug Administration, Rockville, MD, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 25 pgs.	
	15	Parkins *et al.*, "The formulation of biopharmaceutical products," *Pharmaceutical Science & Technology Today*, 3(4):129-137 (2000)	
	16	Randolph *et al.*, "Surfactant-Protein Interactions," *Rational Design of Stable Protein Formulations*, pp. 159-175, Springer, Boston, MA (2002)	
	17	"Phosphate buffer," Cold Spring Harbor Protocols, 2006:pdb.rec8543, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 1 pg.	
	18	LUCENTIS® label, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 14 pgs.	
	19	AVASTIN® label, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 37 pgs.	
	20	REMICADE® label, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 58 pgs.	
	21	XOLAIR® label, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 17 pgs.	
	22	RAPTIVA® label, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 36 pgs.	
	23	SIMULECT® label, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 7 pgs.	
	24	HERCEPTIN® label, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 2 pgs.	
	25	Andersen *et al.*, "Recombinant protein expression for therapeutic applications," *Current Opinion in Biotechnology*, 13:117-123 (2002)	
	26	Janeway *et al.*, "The structure of a typical antibody molecule," Immunobiology: The Immune System in Health and Disease, 5th edition, New York: Garland Science, 6 pgs. (2001)	
	27	Drug Vehicle (Code C927), National Cancer Institute (NCI), retrieved January 6, 2021, from <https://ncithesaurus.nci.nih.gov/ncitbrowser/ConceptReport j sp?dictionary=NCI_Thesaurus&ns=ncit&code=C927 >, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 2 pgs.	

Examiner Signature		Date Considered	

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Receipt date: 03/02/2021

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/739,559
				Filing Date	2020-01-20
				First Named Inventor	Eric Furfine
				Art Unit	
				Examiner Name	
Sheet	3	of	3	Attorney Docket Number	REGN-024CON10

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	28	Controls in SCI experiments, RegenBase, retrieved January 6, 2021, from <http://regenbase.org/control-groups.html>, as submitted to the USPTO on January 7, 2021, in *Inter Partes* Review No. IPR2021-00402, 2 pgs.	
	29		

Examiner Signature	/JON M LOCKARD/	Date Considered	03/19/2021

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L./

Receipt date: 04/10/2020

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/739,559
				Filing Date	2020-01-10
				First Named Inventor	Eric Furfine
				Art Unit	1647
				Examiner Name	Jon Lockard
Sheet	1	of	2	Attorney Docket Number	REGN-024CON10

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	**6100071**	2000-08-08	Davis-Smyth et al.	
	2	**6897294**	2005-05-24	Davis-Smyth et al.	
	3	**7052691**	2006-05-30	Sleeman et al.	

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	**20050281831**	2005-12-22	Davis-Smyth et al.	
	2	**20060217311**	2006-09-28	Dix et al.	
	3	**20080085276**	2008-04-10	Wiegand et al.	
	4	**20140012227**	2014-01-09	Sigg et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1	WO 97/04801	1997-02-13	Genentech, Inc.		
	2	JPH11510170	1999-09-07	Genentech, Inc.	See WO 97/04801 for English Equivalent	X
	3	WO 99/62536	1999-12-09	Celtrix Pharmaceuticals, Inc.		
	4	JP 10273450	1998-10-13	Toagosei Co. Ltd.	See WO 99/62536 for English Equivalent	X
	5	WO 99/62536	1999-12-09	Celtrix Pharmaceuticals, Inc.		
	6	JP2002516871	2002-06-11	Celtrix Pharmaceuticals, Inc.	See WO 99/62536 for English Equivalent	X
	7	WO 2004/091658	2004-10-28	Genentech, Inc.		
	8	WO 2005/000895	2005-01-06	Regeneron Pharmaceuticals, Inc.		
	9	WO 2005011734	2005-02-10	Regeneron Pharmaceuticals, Inc.		
	10	WO 2005/020972	2005-03-10	Eyetech Pharmaceuticals, Inc.		
	11	WO 2006/047325	2006-05-04	Genentech, Inc.		
	12	WO 2006/088650	2006-08-24	Regeneron Pharmaceuticals, Inc.		
	13	WO 2006/104852	2006-10-05	Regeneron Pharmaceuticals, Inc.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T

Examiner Signature		Date Considered	

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Receipt date: 04/10/2020

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/739,559
				Filing Date	2020-01-10
				First Named Inventor	Eric Furfine
				Art Unit	
				Examiner Name	
Sheet	2	of	2	Attorney Docket Number	REGN-024CON10

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	1	FRASER, Hamis M., et al., "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produced Prolonged, Dose-Related Suppression of Ovarian Function," (2004) J. Clin. Endocrin. & Metabol. 90(2):1114-1122	
	2	ANONYMOUS: "Lucentis in the treatment of neovascular (wet) age-related macular degeneration (AMD)", 1 January 2007, pages 1-54	

Examiner Signature	/JON M LOCKARD/	Date Considered	03/19/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L./

PTO/SB/429(08-12)
Approved for use through 07/31/2015. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16739559

U.S. PATENTS				
Cite No	Patent Number	Kind Code[1]	Issue Date (YYYY-MM-DD)	First Named Inventor
1	9580489		2017-02-28	Eric FURFINE
2	7608261		2009-10-27	Eric Furfine
3	9340594		2016-05-17	Eric FURFINE

U.S. PATENT APPLICATION PUBLICATIONS				
Cite No	Publication Number	Kind Code[1]	Publication Date (YYYY-MM-DD)	First Named Inventor

FOREIGN PATENTS AND PUBLISHED FOREIGN PATENT APPLICATIONS						
Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[1]	Publication Date (YYYY-MM-DD)	Applicant, Patentee or First Named Inventor	T[5]
1	WO2000075319	WO		2000-12-14	Nicholas J. Papadopoulos	☐

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16739559

2	WO1998045331	WO		1998-10-15	Manuel Baca	☐

NON-PATENT PUBLICATIONS (e.g., journal article, Office action)

Cite No	Author (if any), title of the publication, page(s) being submitted, publication date, publisher (where available), place of publication (where available).	T[5]	E[6]
1	Ex Parte Request for Reexamination of US10464992, pages 1-70, published 02/11/2020, USPTO, PUBLIC PAIR	☐	☒
2	USPTO Communication on Ex Parte Reexamination of US10464992, pages 1-12, published 04/01/2020, USPTO, PUBLIC PAIR	☐	☒

STATEMENTS

The party making the submission is not an individual who has a duty to disclose information with respect to the above-identified application under 37 CFR 1.56.

This submission complies with the requirements of 35 U.S.C. 122(e) and 37 CFR 1.290.

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16739559

☒ The fee set forth in 37 CFR 1.290(f) has been submitted herewith.

☐ The fee set forth in 37 CFR 1.290(f) is not required because this submission lists three or fewer total items and, to the knowledge of the person signing the statement after making reasonable inquiry, this submission is the first and the only submission under 35 U.S.C 122(e) filed in the above-identified application by the party making the submission or by a party in privity with the party.

☐ This resubmission is being made responsive to a notification of non-compliance issued for an earlier filed third-party submission. The corrections in this resubmission are limited to addressing the non-compliance. As such, the party making this resubmission: (1) requests that the Office apply the previously-paid fee set forth in 37 CFR 1.290(f), or (2) states that no fee is required to accompany this resubmission as the undersigned is again making the fee exemption statement set forth in 37 CFR 1.290(g).

Signature	/NGAM FUNG DAVID CHAN/		
Name/Print	NGAM FUNG DAVID CHAN	Registration Number (if applicable)	76820

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EAST Search History

EAST Search History (Prior Art) /J.L./

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	170	vegfr1r2$ and formulation	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/03/19 22:07
L2	81	L1 and (ophthalmic or intravitreal)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/03/19 22:07
L3	295	(vegf adj (trap or antagonist)) same ophthalmic	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/03/19 22:07
L4	68	L3 same formulation	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/03/19 22:07
L5	137	L2 or L4	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/03/19 22:07
L6	15	L5 and (ophthalmic adj formulation).clm.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/03/19 22:07
L7	1,171	(furfine-e$ dix-d$ graham-k$ frye-k$).in.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/03/19 22:07
L8	10	L6 and L7	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2021/03/19 22:07

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Inventor Information for 16/739559

/J.L./

Inventor Name	City	State/Country
FURFINE, ERIC	CONCORD	MASSACHUSETTS
DIX, DANIEL	LAGRANGEVILLE	NEW YORK
GRAHAM, KENNETH	PLEASANT VALLEY	NEW YORK
FRYE, KELLY	MENDHAM	NEW JERSEY

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | **Inventors** | Applicants | Address | Fees | Post Info | Pre Gra

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(FILE 'HOME' ENTERED AT 22:34:45 ON 19 MAR 2021)

FILE 'MEDLINE, SCISEARCH, EMBASE, BIOSIS' ENTERED AT 22:34:51 ON 19 MAR 2021

L1	0	S	VEGFR1R2
L2	46	S	(VEGF (W) (TRAP OR ANTAGONIST)) (S) OPHTHALMIC
L3	3	S	L2 AND FORMULATION
L4	3	DUP REM	L3 (0 DUPLICATES REMOVED)
L5	14674	S	AFLIBERCEPT OR TRAP-EYE
L6	52	S	L5 (S) FORMULATION
L7	27	DUP REM	L6 (25 DUPLICATES REMOVED)
		E	FURFINE E/AU
L8	336	S	E3-E8
		E	DIX D/AU
L9	427	S	E3-E6 OR E25-E26
		E	GRAHAM K/AU
L10	1083	S	E3 OR E10 OR E149 OR E152
		E	FRYE K/AU
L11	69	S	E3 OR E21
L12	55	S	L2 OR L5 AND (L8 OR L9 OR L10 OR L11)
L13	48	DUP REM	L12 (7 DUPLICATES REMOVED)
L14	75	S	L4 OR L7 OR L13
L15	74	DUP REM	L14 (1 DUPLICATE REMOVED)

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APPLICANTS

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY;

INVENTORS

Eric FURFINE, Concord, MA;
Daniel DIX, LaGrangeville, NY;
Kenneth GRAHAM, Pleasant Valley, NY;
Kelly FRYE, Mendham, NJ;

**** CONTINUING DATA ***************************

This application is a CON of 16/582,486 09/25/2019
which is a CON of 16/159,269 10/12/2018 PAT 10464992
which is a CON of 15/879,294 01/24/2018 PAT 10400025
which is a CON of 15/095,606 04/11/2016 PAT 9914763
which is a CON of 14/330,096 07/14/2014 PAT 9340594
which is a CON of 13/914,996 06/11/2013 PAT 8802107
which is a CON of 13/329,770 12/19/2011 PAT 8481046
which is a CON of 12/833,417 07/09/2010 PAT 8092803
which is a CON of 12/560,885 09/16/2009 PAT 7807164
which is a DIV of 11/818,463 06/14/2007 PAT 7608261
which claims benefit of 60/814,484 06/16/2006

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

01/22/2020

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /JON MCCLELLAND LOCKARD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
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ADDRESS

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065
UNITED STATES

TITLE

VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

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1720	No._____ for following:	❑ Other _____ ❑ Credit

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/739,559
				Filing Date	2020-01-20
				First Named Inventor	Eric Furfine
				Art Unit	
				Examiner Name	
Sheet	1	of	3	Attorney Docket Number	REGN-024CON10

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Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
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	1	W0 97/04801	02/13/1997	Genetech, Inc.		
	2					

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				First Named Inventor	Eric Furfine
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(71) Applicant: GENENTECH, INC. [US/US]; 460 Point San Bruno Boulevard, South San Francisco, CA 94080-4990 (US).

(72) Inventors: ANDYA, James; Apartment D, 227 Richmond Drive, Millbrae, CA 94030 (US). CLELAND, Jeffrey, L.; 844 Cordilleras Avenue, San Carlos, CA 94070 (US). HSU, Chung, C.; 13120 Delson Court, Los Altos Hills, CA 94022 (US). LAM, Xanthe, M.; 280 Denslowe Drive, San Francisco, CA 94132 (US). OVERCASHIER, David, E.; 130 Vallejo Street, El Granada, CA 94018 (US). SHIRE, Steven, J.; 2417 Lincoln Avenue, Belmont, CA 94002 (US). YANG, Janet, Yu-Feng; 1860 Dale Avenue, San Mateo, CA 94401 (US). WU, Sylvia, Sau-Yan; 1438 Filbert Street #203, San Francisco, CA 94109 (US).

(74) Agents: LEE, Wendy, M. et al.; Genentech, Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080-4990 (US).

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(54) Title: STABILE ISOTONIC LYOPHILIZED PROTEIN FORMULATION

(57) Abstract

A stable lyophilized protein formulation is described which can be reconstituted with a suitable diluent to generate a high protein concentration reconstituted formulation which is suitable for subcutaneous administration. For example, anti-IgE and anti-HER2 antibody formulations have been prepared by lyophilizing these antibodies in the presence of a lyoprotectant. The lyophilized mixture thus formed is reconstituted to a high protein concentration without apparent loss of stability of the protein.

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Stabile isotonic lyophilized protein formulation

Background of the Invention

Field of the Invention

This invention is directed to a lyophilized protein formulation. In particular, it relates to a stable lyophilized protein formulation which can be reconstituted with a diluent to generate a stable reconstituted formulation suitable for subcutaneous administration.

Description of Related Disclosures

In the past ten years, advances in biotechnology have made it possible to produce a variety of proteins for pharmaceutical applications using recombinant DNA techniques. Because proteins are larger and more complex than traditional organic and inorganic drugs (*i.e.* possessing multiple functional groups in addition to complex three-dimensional structures), the formulation of such proteins poses special problems. For a protein to remain biologically active, a formulation must preserve intact the conformational integrity of at least a core sequence of the protein's amino acids while at the same time protecting the protein's multiple functional groups from degradation. Degradation pathways for proteins can involve chemical instability (*i.e.* any process which involves modification of the protein by bond formation or cleavage resulting in a new chemical entity) or physical instability (*i.e.* changes in the higher order structure of the protein). Chemical instability can result from deamidation, racemization, hydrolysis, oxidation, beta elimination or disulfide exchange. Physical instability can result from denaturation, aggregation, precipitation or adsorption, for example. The three most common protein degradation pathways are protein aggregation, deamidation and oxidation. Cleland *et al. Critical Reviews in Therapeutic Drug Carrier Systems* 10(4): 307-377 (1993).

Freeze-drying is a commonly employed technique for preserving proteins which serves to remove water from the protein preparation of interest. Freeze-drying, or lyophilization, is a process by which the material to be dried is first frozen and then the ice or frozen solvent is removed by sublimation in a vacuum environment. An excipient may be included in pre-lyophilized formulations to enhance stability during the freeze-drying process and/or to improve stability of the lyophilized product upon storage. Pikal, M. *Biopharm.* 3(9)26-30 (1990) and Arakawa *et al. Pharm. Res.* 8(3):285-291 (1991).

It is an object of the present invention to provide a lyophilized protein formulation which is stable upon storage and delivery. It is a further object to provide a stable reconstituted protein formulation which is suitable for subcutaneous administration. In certain embodiments, it is an object to provide a multi-use formulation which is stable for at least the time over which it will be administered to a patient.

Summary of the Invention

This invention is based on the discovery that a stable lyophilized protein formulation can be prepared using a lyoprotectant (preferably a sugar such as sucrose or trehalose), which lyophilized formulation can be reconstituted to generate a stable reconstituted formulation having a protein concentration which is significantly higher (*e.g.* from about 2-40 times higher, preferably 3-10 times higher and most preferably 3-6 times higher) than the protein concentration in the pre-lyophilized formulation. In particular, while the protein concentration in the pre-lyophilized formulation may be 5 mg/mL or less, the protein concentration in the reconstituted formulation is generally 50 mg/mL or more. Such high protein concentrations in the reconstituted formulation are considered to be particularly useful where the formulation is intended for subcutaneous administration.

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Despite the very high protein concentration in the reconstituted formulation, it has been found that the reconstituted formulation is stable (*i.e.* fails to display significant or unacceptable levels of chemical or physical instability of the protein) at 2-8°C for at least about 30 days. In certain embodiments, the reconstituted formulation is isotonic. In spite of the use of lower concentrations of the lyoprotectant to achieve such isotonic formulations upon reconstitution, it was discovered herein that the protein in the lyophilized formulation essentially retains its physical and chemical stability and integrity upon lyophilization and storage.

When reconstituted with a diluent comprising a preservative (such as bacteriostatic water for injection, BWFI), the reconstituted formulation may be used as a multi-use formulation. Such a formulation is useful, for example, where the patient requires frequent subcutaneous administrations of the protein to treat a chronic medical condition. The advantage of a multi-use formulation is that it facilitates ease of use for the patient, reduces waste by allowing complete use of vial contents, and results in a significant cost savings for the manufacturer since several doses are packaged in a single vial (lower filling and shipping costs).

Based on the observations described herein, in one aspect the invention provides a stable isotonic reconstituted formulation comprising a protein in an amount of at least about 50 mg/mL and a diluent, which reconstituted formulation has been prepared from a lyophilized mixture of a protein and a lyoprotectant, wherein the protein concentration in the reconstituted formulation is about 2-40 times greater than the protein concentration in the mixture before lyophilization.

In another embodiment, the invention provides a stable reconstituted formulation comprising an antibody in an amount of at least about 50 mg/mL and a diluent, which reconstituted formulation has been prepared from a lyophilized mixture of an antibody and a lyoprotectant, wherein the antibody concentration in the reconstituted formulation is about 2-40 times greater than the antibody concentration in the mixture before lyophilization.

The ratio of lyoprotectant:protein in the lyophilized formulation of the preceding paragraphs depends, for example, on both the protein and lyoprotectant of choice, as well as the desired protein concentration and isotonicity of the reconstituted formulation. In the case of a full length antibody (as the protein) and trehalose or sucrose (as the lyoprotectant) for generating a high protein concentration isotonic reconstituted formulation, the ratio may, for example, be about 100-1500 mole trehalose or sucrose:1 mole antibody.

Generally, the pre-lyophilized formulation of the protein and lyoprotectant will further include a buffer which provides the formulation at a suitable pH, depending on the protein in the formulation. For this purpose, it has been found to be desirable to use a histidine buffer in that, as demonstrated below, this appears to have lyoprotective properties.

The formulation may further include a surfactant (*e.g.* a polysorbate) in that it has been observed herein that this can reduce aggregation of the reconstituted protein and/or reduce the formation of particulates in the reconstituted formulation. The surfactant can be added to the pre-lyophilized formulation, the lyophilized formulation and/or the reconstituted formulation (but preferably the pre-lyophilized formulation) as desired.

The invention further provides a method for preparing a stable isotonic reconstituted formulation comprising reconstituting a lyophilized mixture of a protein and a lyoprotectant in a diluent such that the protein concentration in the reconstituted formulation is at least 50 mg/mL, wherein the protein concentration in the

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reconstituted formulation is about 2-40 times greater than the protein concentration in the mixture before lyophilization.

In yet a further embodiment, the invention provides a method for preparing a formulation comprising the steps of: (a) lyophilizing a mixture of a protein and a lyoprotectant; and (b) reconstituting the lyophilized mixture of step (a) in a diluent such that the reconstituted formulation is isotonic and stable and has a protein concentration of at least about 50 mg/mL. For example, the protein concentration in the reconstituted formulation may be from about 80 mg/mL to about 300 mg/mL. Generally, the protein concentration in the reconstituted formulation is about 2-40 times greater than the protein concentration in the mixture before lyophilization.

An article of manufacture is also provided herein which comprises: (a) a container which holds a lyophilized mixture of a protein and a lyoprotectant; and (b) instructions for reconstituting the lyophilized mixture with a diluent to a protein concentration in the reconstituted formulation of at least about 50 mg/mL. The article of manufacture may further comprise a second container which holds a diluent (*e.g.* bacteriostatic water for injection (BWFI) comprising an aromatic alcohol).

The invention further provides a method for treating a mammal comprising administering a therapeutically effective amount of a reconstituted formulation disclosed herein to a mammal, wherein the mammal has a disorder requiring treatment with the protein in the formulation. For example, the formulation may be administered subcutaneously.

One useful anti-HER2 antibody pre-lyophilized formulation as discovered in the experiments detailed below was found to comprise anti-HER2 in amount from about 5-40 mg/mL (*e.g.* 20-30 mg/mL) and sucrose or trehalose in an amount from about 10-100 mM (*e.g.* 40-80 mM), a buffer (*e.g.* histidine, pH 6 or succinate, pH 5) and a surfactant (*e.g.* a polysorbate). The lyophilized formulation was found to be stable at 40°C for at least 3 months and stable at 30°C for at least 6 months. This anti-HER2 formulation can be reconstituted with a diluent to generate a formulation suitable for intravenous administration comprising anti-HER2 in an amount from about 10-30 mg/mL which is stable at 2-8°C for at least about 30 days. Where higher concentrations of the anti-HER2 antibody are desired (for example where subcutaneous delivery of the antibody is the intended mode of administration to the patient), the lyophilized formulation may be reconstituted to yield a stable reconstituted formulation having a protein concentration of 50 mg/mL or more.

One desirable anti-IgE antibody pre-lyophilized formulation discovered herein has anti-IgE in amount from about 5-40 mg/mL (*e.g.* 20-30 mg/mL) and sucrose or trehalose in an amount from about 60-300 mM (*e.g.* 80-170 mM), a buffer (preferably histidine, pH 6) and a surfactant (such as a polysorbate). The lyophilized anti-IgE formulation is stable at 30°C for at least 1 year. This formulation can be reconstituted to yield a formulation comprising anti-IgE in an amount from about 15-45 mg/mL (*e.g.* 15-25 mg/mL) suitable for intravenous administration which is stable at 2-8°C for at least 1 year. Alternatively, where higher concentrations of anti-IgE in the formulation are desired, the lyophilized formulation can be reconstituted in order to generate a stable formulation having an anti-IgE concentration of ≥50 mg/mL.

Brief Description of the Drawings

Figure 1 shows the effect of reconstitution volume on the stability of lyophilized rhuMAb HER2. The lyophilized formulation was prepared from a pre-lyophilization formulation comprising 25 mg/mL protein, 60

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mM trehalose, 5 mM sodium succinate, pH 5.0, and 0.01% Tween 20™. The lyophilized cake was incubated at 40° C and then reconstituted with 4.0 (○) or 20.0 mL (●) of BWFI. The fraction of intact protein in the reconstituted formulation was measured by native size exclusion chromatography and defined as the peak area of the native protein relative to the total peak area including aggregates.

Figure 2 illustrates the effect of trehalose concentration on the stability of lyophilized rhuMAb HER2. The protein was lyophilized at 25 mg/mL in 5 mM sodium succinate, pH 5.0 (circles) or 5 mM histidine, pH 6.0 (squares) and trehalose concentrations ranging from 60 mM (360 molar ratio) to 200 mM (1200 molar ratio). The lyophilized protein was incubated at 40° C for either 30 days (closed symbols) or 91 days (open symbols). The amount of intact protein was measured after reconstitution of the lyophilized protein with 20 mL BWFI.

Figure 3 demonstrates the effect of trehalose concentration on the long term stability of lyophilized rhuMAb HER2 stored at 40° C. The protein was lyophilized at either 25 mg/mL in 5 mM sodium succinate, pH 5.0, 0.01% Tween 20™, and 60 mM trehalose (■) or 5 mM histidine, pH 6.0, 0.01% Tween 20™, and 60 mM trehalose (□) or 21 mg/mL in 10 mM sodium succinate, pH 5.0, 0.2% Tween 20™ and 250 mM trehalose (●). The lyophilized protein was incubated at 40° C and then reconstituted with 20 mL of BWFI. The amount of intact protein was measured after reconstitution.

Figure 4 shows the stability of rhuMAb HER2 lyophilized in 38.4 mM mannitol (7 mg/mL), 20.4 mM sucrose (7 mg/mL), 5 mM histidine, pH 6.0, 0.01% Tween 20™. The lyophilized protein was incubated at 40° C and then reconstituted with either 4.0 mL (○) or 20 mL (●) of BWFI. The amount of intact protein was measured after reconstitution.

Figure 5 demonstrates stability of reconstituted rhuMAb HER2 lyophilized in 5 mM sodium succinate, pH 5.0, 60 mM trehalose, 0.01% Tween 20™. Samples were reconstituted with either 4.0 mL (squares) or 20.0 mL (circles) of BWFI (20 mL:0.9% benzyl alcohol; 4 mL:1.1% benzyl alcohol) and then stored at 5° C (solid symbols) or 25° C (open symbols). The % native protein was defined as the peak area of the native (not degraded) protein relative to the total peak area as measured by cation exchange chromatography.

Figure 6 shows stability of reconstituted rhuMAb HER2 lyophilized in 5 mM histidine, pH 6.0, 60 mM trehalose, 0.01% Tween 20. Samples were reconstituted with either 4.0 mL (squares) or 20.0 mL (circles) of BWFI (20 mL:0.9% benzyl alcohol; 4 mL:1.1% benzyl alcohol) and then stored at 5° C (solid symbols) or 25 ° C (open symbols). The % native protein was defined as the peak area of the native (not degraded) protein relative to the total peak area as measured by cation exchange chromatography.

Figure 7 reveals stability of reconstituted rhuMAb HER2 lyophilized in 5 mM histidine, pH 6.0, 38.4 mM mannitol, 20.4 mM sucrose, 0.01% Tween 20. Samples were reconstituted with either 4.0 mL (squares) or 20.0 mL (circles) of BWFI (20 mL:0.9% benzyl alcohol; 4 mL:1.1% benzyl alcohol) and then stored at 5° C (solid symbols) or 25 ° C (open symbols). The % native protein was defined as the peak area of the native (not degraded) protein relative to the total peak area as measured by cation exchange chromatography.

Figure 8 shows stability of reconstituted rhuMAb HER2 lyophilized in 10 mM sodium succinate, pH 5.0, 250 mM trehalose, 0.2% Tween 20. Samples were reconstituted with 20.0 mL of BWFI (0.9% benzyl alcohol) and then stored at 5° C (●) or 25 ° C (○). The % native protein was defined as the peak area of the native (not degraded) protein relative to the total peak area as measured by cation exchange chromatography.

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Figure 9 shows aggregation of rhuMAb E25 formulated into buffers ranging from pH 5 to pH 7 at 10 mM buffer concentration and 5 mg/mL antibody concentration. Samples were lyophilized and assayed at time zero and after 4 weeks, 8 weeks, and 52 weeks of storage at 2-8°C. The buffers were: potassium phosphate pH 7.0 (○); sodium phosphate pH 7.0 (□); histidine pH 7.0 (◇); sodium succinate pH 6.5 (●); sodium succinate pH 6.0 (■); sodium succinate pH 5.5 (♦); and sodium succinate pH 5.0 (▲).

Figure 10 depicts aggregation of rhuMAb E25 lyophilized in 5 mM histidine buffer at both pH 6 and pH 7 and assayed following storage as follows. The buffer was at: pH 6.0 stored at 2-8°C (○); pH 6 stored at 25°C (□); pH 6 stored at 40°C (◇); pH 7 stored at 2-8°C (●); pH 7 stored at 25°C (■); and pH 7 stored at 40°C (♦).

Figure 11 illustrates aggregation of 5 mg/mL rhuMAb E25 formulated into 10 mM sodium succinate at pH 5.0 with lyoprotectant added at a concentration of 275 mM (isotonic). The lyoprotectants were: control, no lyoprotectant (○); mannitol (□); lactose (◇); maltose (●); trehalose (■); and sucrose (♦). Samples were lyophilized and assayed at time zero and after 4 weeks, 8 weeks, and 52 weeks of storage at 2-8°C.

Figure 12 shows aggregation of 5 mg/mL rhuMAb E25 formulated into 10 mM sodium succinate at pH 5.0 with lyoprotectant added at a concentration of 275 mM (isotonic). The lyoprotectants were: control, no lyoprotectant (○); mannitol (□); lactose (◇); maltose (●); trehalose (■); and sucrose (♦). Samples were lyophilized and assayed at time zero and after 4 weeks, 8 weeks, and 52 weeks of storage at 40°C.

Figure 13 depicts hydrophobic interaction chromatography of 20 mg/mL rhuMAb E25 lyophilized in histidine buffer at pH 6 with an isotonic concentration (*i.e.* 275 mM) of lactose stored for 24 weeks at 2-8, 25 or 40°C and reconstituted to 20 mg/mL.

Figure 14 shows hydrophobic interaction chromatography of 20 mg/mL rhuMAb E25 lyophilized in histidine buffer at pH 6 stored for 24 weeks at 2-8, 25 or 40°C and reconstituted to 20 mg/mL.

Figure 15 illustrates hydrophobic interaction chromatography of 20 mg/mL rhuMAb E25 lyophilized in histidine buffer at pH 6 with an isotonic concentration (*i.e.* 275 mM) of sucrose and stored for 24 weeks at 2-8, 25 or 40°C and reconstituted to 20 mg/mL.

Figure 16 illustrates the effect of sugar concentration on rhuMAb E25 formulated at 20 mg/mL in 5 mM histidine at pH 6.0. Sucrose (●) and trehalose (□) were added to the formulation at molar ratios ranging from 0 to 2010 (isotonic) (see Table 1 below). Samples were lyophilized and assayed after 12 weeks of storage at 50°C.

TABLE 1

Moles of Sugar: E25 antibody	Sugar conc. (mM)
0	0
260	34.4
380	51.6
510	68.8
760	103.1
1020	137.5
1530	206.3

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2010	275

Figure 17 reveals aggregation of rhuMAb E25 formulated at 25 mg/mL into 5 mM histidine at pH 6 with 85 mM sucrose (○); 85 mM trehalose (□); 161 mM sucrose (♦) or 161 mM trehalose (▲). Samples were lyophilized and stored at 2-8° C followed by reconstitution with 0.9% benzyl alcohol to 100 mg/mL antibody in 20 mM histidine at pH 6 with isotonic (340 mM) and hypertonic (644 mM) sugar concentration.

Figure 18 shows aggregation of rhuMAb E25 formulated at 25 mg/mL into 5 mM histidine at pH 6 with 85 mM sucrose (○); 85 mM trehalose (□); 161 mM sucrose (♦) or 161 mM trehalose (▲). Samples were lyophilized and stored at 30° C followed by reconstitution with 0.9% benzyl alcohol to 100 mg/mL antibody in 20 mM histidine at pH 6 with isotonic (340 mM) and hypertonic (644 mM) sugar concentration.

Figure 19 illustrates aggregation of rhuMAb E25 formulated at 25 mg/mL into 5 mM histidine at pH 6 with 85 mM sucrose (○); 85 mM trehalose (□); 161 mM sucrose (♦) or 161 mM trehalose (▲). Samples were lyophilized and stored at 50° C followed by reconstitution with 0.9% benzyl alcohol to 100 mg/mL antibody in 20 mM histidine at pH 6 with isotonic (340 mM) and hypertonic (644 mM) sugar concentration.

Detailed Description of the Preferred Embodiments

I. Definitions

By "protein" is meant a sequence of amino acids for which the chain length is sufficient to produce the higher levels of tertiary and/or quaternary structure. This is to distinguish from "peptides" or other small molecular weight drugs that do not have such structure. Typically, the protein herein will have a molecular weight of at least about 15-20 kD, preferably at least about 20 kD.

Examples of proteins encompassed within the definition herein include mammalian proteins, such as, *e.g.*, growth hormone, including human growth hormone and bovine growth hormone; growth hormone releasing factor; parathyroid hormone; thyroid stimulating hormone; lipoproteins; α-1-antitrypsin; insulin A-chain; insulin B-chain; proinsulin; follicle stimulating hormone; calcitonin; luteinizing hormone; glucagon; clotting factors such as factor VIIIC, factor IX, tissue factor, and von Willebrands factor; anti-clotting factors such as Protein C; atrial natriuretic factor; lung surfactant; a plasminogen activator, such as urokinase or tissue-type plasminogen activator (t-PA); bombazine; thrombin; tumor necrosis factor-α and -β; enkephalinase; RANTES (regulated on activation normally T-cell expressed and secreted); human macrophage inflammatory protein (MIP-1-α); serum albumin such as human serum albumin; mullerian-inhibiting substance; relaxin A-chain; relaxin B-chain; prorelaxin; mouse gonadotropin-associated peptide; DNase; inhibin; activin; vascular endothelial growth factor (VEGF); receptors for hormones or growth factors; an integrin; protein A or D; rheumatoid factors; a neurotrophic factor such as bone-derived neurotrophic factor (BDNF), neurotrophin-3, -4, -5, or -6 (NT-3, NT-4, NT-5, or NT-6), or a nerve growth factor such as NGF-β; platelet-derived growth factor (PDGF); fibroblast growth factor such as aFGF and bFGF; epidermal growth factor (EGF); transforming growth factor (TGF) such as TGF-α and TGF-β, including TGF-β1, TGF-β2, TGF-β3, TGF-β4, or TGF-β5; insulin-like growth factor-I and -II (IGF-I and IGF-II); des(1-3)-IGF-I (brain IGF-I); insulin-like growth factor binding proteins; CD proteins such as CD3, CD4, CD8, CD19 and CD20; erythropoietin (EPO); thrombopoietin (TPO); osteoinductive factors; immunotoxins; a bone morphogenetic protein (BMP); an interferon such as interferon-α, -β, and -γ; colony stimulating factors (CSFs), *e.g.*, M-CSF, GM-CSF, and G-CSF; interleukins (ILs), *e.g.*, IL-1 to IL-10; superoxide

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dismutase; T-cell receptors; surface membrane proteins; decay accelerating factor (DAF); a viral antigen such as, for example, a portion of the AIDS envelope; transport proteins; homing receptors; addressins; regulatory proteins; immunoadhesins; antibodies; and biologically active fragments or variants of any of the above-listed polypeptides.

The protein which is formulated is preferably essentially pure and desirably essentially homogeneous (*i.e.* free from contaminating proteins etc). "Essentially pure" protein means a composition comprising at least about 90% by weight of the protein, based on total weight of the composition, preferably at least about 95% by weight. "Essentially homogeneous" protein means a composition comprising at least about 99% by weight of protein, based on total weight of the composition.

In certain embodiments, the protein is an antibody. The antibody may bind to any of the above-mentioned molecules, for example. Exemplary molecular targets for antibodies encompassed by the present invention include CD proteins such as CD3, CD4, CD8, CD19, CD20 and CD34; members of the HER receptor family such as the EGF receptor, HER2, HER3 or HER4 receptor; cell adhesion molecules such as LFA-1, Mo1, p150,95, VLA-4, ICAM-1, VCAM and αv/β3 integrin including either α or β subunits thereof (*e.g.* anti-CD11a, anti-CD18 or anti-CD11b antibodies); growth factors such as VEGF; IgE; blood group antigens; flk2/flt3 receptor; obesity (OB) receptor; protein C etc.

The term "antibody" is used in the broadest sense and specifically covers monoclonal antibodies (including full length antibodies which have an immunoglobulin Fc region), antibody compositions with polyepitopic specificity, bispecific antibodies, diabodies, and single-chain molecules, as well as antibody fragments (*e.g.*, Fab, $F(ab')_2$, and Fv).

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler *et al., Nature*, 256: 495 (1975), or may be made by recombinant DNA methods (see, *e.g.*, U.S. Patent No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson *et al., Nature,* 352:624-628 (1991) and Marks *et al., J. Mol. Biol.*, 222:581-597 (1991), for example.

The monoclonal antibodies herein specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from

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another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567; Morrison *et al., Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984)).

"Humanized" forms of non-human (*e.g.*, murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementarity determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and optimize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones *et al., Nature*, 321:522-525 (1986); Reichmann *et al., Nature*, 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.*, 2:593-596 (1992). The humanized antibody includes a Primatized™ antibody wherein the antigen-binding region of the antibody is derived from an antibody produced by immunizing macaque monkeys with the antigen of interest.

A "stable" formulation is one in which the protein therein essentially retains its physical and chemical stability and integrity upon storage. Various analytical techniques for measuring protein stability are available in the art and are reviewed in *Peptide and Protein Drug Delivery*, 247-301, Vincent Lee Ed., Marcel Dekker, Inc., New York, New York, Pubs. (1991) and Jones, A. *Adv. Drug Delivery Rev.* 10: 29-90 (1993). Stability can be measured at a selected temperature for a selected time period. For rapid screening, the formulation may be kept at 40°C for 2 weeks to 1 month, at which time stability is measured. Where the formulation is to be stored at 2-8°C, generally the formulation should be stable at 30°C or 40°C for at least 1 month and/or stable at 2-8°C for at least 2 years. Where the formulation is to be stored at 30°C, generally the formulation should be stable for at least 2 years at 30°C and/or stable at 40°C for at least 6 months. For example, the extent of aggregation following lyophilization and storage can be used as an indicator of protein stability (see Examples herein). For example, a "stable" formulation may be one wherein less than about 10% and preferably less than about 5% of the protein is present as an aggregate in the formulation. In other embodiments, any increase in aggregate formation following lyophilization and storage of the lyophilized formulation can be determined. For example, a "stable" lyophilized formulation may be one wherein the increase in aggregate in the lyophilized formulation is less than about 5% and preferably less than about 3%, when the lyophilized formulation is stored at 2-8° C for at least one year. In other embodiments, stability of the protein formulation may be measured using a biological activity assay (see, *e.g.*, Example 2 below).

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A "reconstituted" formulation is one which has been prepared by dissolving a lyophilized protein formulation in a diluent such that the protein is dispersed in the reconstituted formulation. The reconstituted formulation in suitable for administration (*e.g.* parenteral administration) to a patient to be treated with the protein of interest and, in certain embodiments of the invention, may be one which is suitable for subcutaneous administration.

By "isotonic" is meant that the formulation of interest has essentially the same osmotic pressure as human blood. Isotonic formulations will generally have an osmotic pressure from about 250 to 350mOsm. Isotonicity can be measured using a vapor pressure or ice-freezing type osmometer, for example.

A "lyoprotectant" is a molecule which, when combined with a protein of interest, significantly prevents or reduces chemical and/or physical instability of the protein upon lyophilization and subsequent storage. Exemplary lyoprotectants include sugars such as sucrose or trehalose; an amino acid such as monosodium glutamate or histidine; a methylamine such as betaine; a lyotropic salt such as magnesium sulfate; a polyol such as trihydric or higher sugar alcohols, *e.g.* glycerin, erythritol, glycerol, arabitol, xylitol, sorbitol, and mannitol; propylene glycol; polyethylene glycol; Pluronics; and combinations thereof. The preferred lyoprotectant is a non-reducing sugar, such as trehalose or sucrose.

The lyoprotectant is added to the pre-lyophilized formulation in a "lyoprotecting amount" which means that, following lyophilization of the protein in the presence of the lyoprotecting amount of the lyoprotectant, the protein essentially retains its physical and chemical stability and integrity upon lyophilization and storage.

The "diluent" of interest herein is one which is pharmaceutically acceptable (safe and non-toxic for administration to a human) and is useful for the preparation of a reconstituted formulation. Exemplary diluents include sterile water, bacteriostatic water for injection (BWFI), a pH buffered solution (*e.g.* phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution.

A "preservative" is a compound which can be added to the diluent to essentially reduce bacterial action in the reconstituted formulation, thus facilitating the production of a multi-use reconstituted formulation, for example. Examples of potential preservatives include octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride (a mixture of alkylbenzyldimethylammonium chlorides in which the alkyl groups are long-chain compounds), and benzethonium chloride. Other types of preservatives include aromatic alcohols such as phenol, butyl and benzyl alcohol, alkyl parabens such as methyl or propyl paraben, catechol, resorcinol, cyclohexanol, 3-pentanol, and m-cresol. The most preferred preservative herein is benzyl alcohol.

A "bulking agent" is a compound which adds mass to the lyophilized mixture and contributes to the physical structure of the lyophilized cake (*e.g.* facilitates the production of an essentially uniform lyophilized cake which maintains an open pore structure). Exemplary bulking agents include mannitol, glycine, polyethylene glycol and xorbitol.

"Treatment" refers to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include those already with the disorder as well as those in which the disorder is to be prevented.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, *etc.* Preferably, the mammal is human.

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A "disorder" is any condition that would benefit from treatment with the protein. This includes chronic and acute disorders or diseases including those pathological conditions which predispose the mammal to the disorder in question. Non-limiting examples of disorders to be treated herein include carcinomas and allergies.

II. Modes for Carrying out the Invention

A. Protein Preparation

The protein to be formulated is prepared using techniques which are well established in the art including synthetic techniques (such as recombinant techniques and peptide synthesis or a combination of these techniques) or may be isolated from an endogenous source of the protein. In certain embodiments of the invention, the protein of choice is an antibody. Techniques for the production of antibodies follow.

(i) Polyclonal antibodies.

Polyclonal antibodies are generally raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen to a protein that is immunogenic in the species to be immunized, *e.g.*, keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor using a bifunctional or derivatizing agent, for example, maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, $SOCl_2$, or $R^1N=C=NR$, where R and R^1 are different alkyl groups.

Animals are immunized against the antigen, immunogenic conjugates, or derivatives by combining 1 mg or 1 μg of the peptide or conjugate (for rabbits or mice, respectively) with 3 volumes of Freund's complete adjuvant. One month later the animals are boosted with 1/5 to 1/10 the original amount of peptide or conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to 14 days later the animals are bled and the serum is assayed for antibody titer. Animals are boosted until the titer plateaus. Preferably, the animal is boosted with the conjugate of the same antigen, but conjugated to a different protein and/or through a different cross-linking reagent. Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating agents such as alum are suitably used to enhance the immune response.

(ii) Monoclonal antibodies.

Monoclonal antibodies are obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Thus, the modifier "monoclonal" indicates the character of the antibody as not being a mixture of discrete antibodies.

For example, the monoclonal antibodies may be made using the hybridoma method first described by Kohler *et al., Nature,* 256:495 (1975), or may be made by recombinant DNA methods (U.S. Patent No. 4,816,567).

In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized as hereinabove described to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, *Monoclonal Antibodies: Principles and Practice*, pp.59-103 (Academic Press, 1986)).

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The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

Preferred myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among these, preferred myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, California USA, and SP-2 cells available from the American Type Culture Collection, Rockville, Maryland USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, *J. Immunol.*, 133:3001 (1984); Brodeur *et al., Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA).

The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson *et al., Anal. Biochem.*, 107:220 (1980).

After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, *Monoclonal Antibodies: Principles and Practice*, pp.59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal.

The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles on recombinant expression in bacteria of DNA encoding the antibody include Skerra *et al., Curr. Opinion in Immunol.*, 5:256-262 (1993) and Plückthun, *Immunol. Revs.*, 130:151-188 (1992).

In a further embodiment, antibodies can be isolated from antibody phage libraries generated using the techniques described in McCafferty *et al., Nature*, 348:552-554 (1990). Clackson *et al., Nature*, 352:624-628 (1991) and Marks *et al., J. Mol. Biol.*, 222:581-597 (1991) describe the isolation of murine and human antibodies, respectively, using phage libraries. Subsequent publications describe the production of high affinity

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(nM range) human antibodies by chain shuffling (Marks *et al.*, *Bio/Technology*, 10:779-783 (1992)), as well as combinatorial infection and *in vivo* recombination as a strategy for constructing very large phage libraries (Waterhouse *et al.*, *Nuc. Acids. Res.*, 21:2265-2266 (1993)). Thus, these techniques are viable alternatives to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies.

The DNA also may be modified, for example, by substituting the coding sequence for human heavy- and light-chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison, *et al.*, *Proc. Natl Acad. Sci. USA*, 81:6851 (1984)), or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide.

Typically such non-immunoglobulin polypeptides are substituted for the constant domains of an antibody, or they are substituted for the variable domains of one antigen-combining site of an antibody to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for an antigen and another antigen-combining site having specificity for a different antigen.

Chimeric or hybrid antibodies also may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide-exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate. *(iii)* *Humanized and human antibodies*.

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers (Jones *et al.*, *Nature*, 321:522-525 (1986); Riechmann *et al.*, *Nature*, 332:323-327 (1988); Verhoeyen *et al.*, *Science*, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important to reduce antigenicity. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable-domain sequences. The human sequence which is closest to that of the rodent is then accepted as the human framework (FR) for the humanized antibody (Sims *et al.*, *J. Immunol.*, 151:2296 (1993); Chothia *et al.*, *J. Mol. Biol.*, 196:901 (1987)). Another method uses a particular framework derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter *et al.*, *Proc. Natl. Acad. Sci. USA*, 89:4285 (1992); Presta *et al.*, *J. Immnol.*, 151:2623 (1993)).

It is further important that antibodies be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method, humanized

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antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, *i.e.*, the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding.

Alternatively, it is now possible to produce transgenic animals (*e.g.*, mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (J_H) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. See, *e.g.*, Jakobovits *et al.*, *Proc. Natl. Acad. Sci. USA*, 90:2551 (1993); Jakobovits *et al.*, *Nature*, 362:255-258 (1993); Bruggermann *et al.*, *Year in Immuno.*, 7:33 (1993). Human antibodies can also be derived from phage-display libraries (Hoogenboom *et al.*, *J. Mol. Biol.*, 227:381 (1991); Marks *et al.*, *J. Mol. Biol.*, 222:581-597 (1991)).

(iv) Bispecific antibodies

Bispecific antibodies (BsAbs) are antibodies that have binding specificities for at least two different epitopes. Such antibodies can be derived from full length antibodies or antibody fragments (*e.g.* $F(ab')_2$ bispecific antibodies).

Methods for making bispecific antibodies are known in the art. Traditional production of full length bispecific antibodies is based on the coexpression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (Millstein *et al.*, *Nature*, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO 93/08829 and in Traunecker *et al.*, *EMBO J.*, 10:3655-3659 (1991).

According to a different approach, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light chain binding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. This provides for great flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in

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the construction provide the optimum yields. It is, however, possible to insert the coding sequences for two or all three polypeptide chains in one expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios are of no particular significance.

In a preferred embodiment of this approach, the bispecific antibodies are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. It was found that this asymmetric structure facilitates the separation of the desired bispecific compound from unwanted immunoglobulin chain combinations, as the presence of an immunoglobulin light chain in only one half of the bispecific molecule provides for a facile way of separation. This approach is disclosed in WO 94/04690 published March 3, 1994. For further details of generating bispecific antibodies see, for example, Suresh *et al., Methods in Enzymology*, 121:210 (1986).

Bispecific antibodies include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (US Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360, WO 92/200373). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in US Patent No. 4,676,980, along with a number of cross-linking techniques.

Techniques for generating bispecific antibodies from antibody fragments have also been described in the literature. The following techniques can also be used for the production of bivalent antibody fragments which are not necessarily bispecific. For example, Fab' fragments recovered from *E. coli* can be chemically coupled *in vitro* to form bivalent antibodies. See, Shalaby *et al., J. Exp. Med.*, 175:217-225 (1992).

Various techniques for making and isolating bivalent antibody fragments directly from recombinant cell culture have also been described. For example, bivalent heterodimers have been produced using leucine zippers. Kostelny *et al., J. Immunol.*, 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. The "diabody" technology described by Hollinger *et al., Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific/bivalent antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific/bivalent antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See Gruber *et al., J. Immunol.*, 152:5368 (1994).

B. Preparation of the Lyophilized Formulation

After preparation of the protein of interest as described above, a "pre-lyophilized formulation" is produced. The amount of protein present in the pre-lyophilized formulation is determined taking into account the desired dose volumes, mode(s) of administration etc. Where the protein of choice is an intact antibody (such as an anti-IgE or anti-HER2 antibody), from about 2 mg/mL to about 50 mg/mL, preferably from about 5 mg/mL to about 40 mg/mL and most preferably from about 20-30 mg/mL is an exemplary starting protein concentration.

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The protein is generally present in solution. For example, the protein may be present in a pH-buffered solution at a pH from about 4-8, and preferably from about 5-7. Exemplary buffers include histidine, phosphate, Tris, citrate, succinate and other organic acids. The buffer concentration can be from about 1 mM to about 20 mM, or from about 3 mM to about 15 mM, depending, for example, on the buffer and the desired isotonicity of the formulation (*e.g.* of the reconstituted formulation). The preferred buffer is histidine in that, as demonstrated below, this can have lyoprotective properties. Succinate was shown to be another useful buffer.

The lyoprotectant is added to the pre-lyophilized formulation. In preferred embodiments, the lyoprotectant is a non-reducing sugar such as sucrose or trehalose. The amount of lyoprotectant in the pre-lyophilized formulation is generally such that, upon reconstitution, the resulting formulation will be isotonic. However, hypertonic reconstituted formulations may also be suitable. In addition, the amount of lyoprotectant must not be too low such that an unacceptable amount of degradation/aggregation of the protein occurs upon lyophilization. Where the lyoprotectant is a sugar (such as sucrose or trehalose) and the protein is an antibody, exemplary lyoprotectant concentrations in the pre-lyophilized formulation are from about 10 mM to about 400 mM, and preferably from about 30 mM to about 300 mM, and most preferably from about 50 mM to about 100 mM.

The ratio of protein to lyoprotectant is selected for each protein and lyoprotectant combination. In the case of an antibody as the protein of choice and a sugar (*e.g.*, sucrose or trehalose) as the lyoprotectant for generating an isotonic reconstituted formulation with a high protein concentration, the molar ratio of lyoprotectant to antibody may be from about 100 to about 1500 moles lyoprotectant to 1 mole antibody, and preferably from about 200 to about 1000 moles of lyoprotectant to 1 mole antibody, for example from about 200 to about 600 moles of lyoprotectant to 1 mole antibody.

In preferred embodiments of the invention, it has been found to be desirable to add a surfactant to the pre-lyophilized formulation. Alternatively, or in addition, the surfactant may be added to the lyophilized formulation and/or the reconstituted formulation. Exemplary surfactants include nonionic surfactants such as polysorbates (*e.g.* polysorbates 20 or 80); poloxamers (*e.g.* poloxamer 188); Triton; sodium dodecyl sulfate (SDS); sodium laurel sulfate: sodium octyl glycoside; lauryl-, myristyl-, linoleyl-, or stearyl-sulfobetaine; lauryl-, myristyl-, linoleyl- or stearyl-sarcosine; linoleyl-, myristyl-, or cetyl-betaine; lauroamidopropyl-, cocamidopropyl-, linoleamidopropyl-, myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-betaine (*e.g.* lauroamidopropyl); myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-dimethylamine; sodium methyl cocoyl-, or disodium methyl oleyl-taurate; and the MONAQUAT™ series (Mona Industries, Inc., Paterson, New Jersey), polyethyl glycol, polypropyl glycol, and copolymers of ethylene and propylene glycol (*e.g.* Pluronics, PF68 etc). The amount of surfactant added is such that it reduces aggregation of the reconstituted protein and minimizes the formation of particulates after reconstitution. For example, the surfactant may be present in the pre-lyophilized formulation in an amount from about 0.001-0.5%, and preferably from about 0.005-0.05%.

In certain embodiments of the invention, a mixture of the lyoprotectant (such as sucrose or trehalose) and a bulking agent (*e.g.* mannitol or glycine) is used in the preparation of the pre-lyophilization formulation. The bulking agent may allow for the production of a uniform lyophilized cake without excessive pockets therein etc.

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Other pharmaceutically acceptable carriers, excipients or stabilizers such as those described in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980) may be included in the pre-lyophilized formulation (and/or the lyophilized formulation and/or the reconstituted formulation) provided that they do not adversely affect the desired characteristics of the formulation. Acceptable carriers, excipients or stabilizers are nontoxic to recipients at the dosages and concentrations employed and include: additional buffering agents; preservatives; co-solvents; antioxidants including ascorbic acid and methionine; chelating agents such as EDTA; metal complexes (*e.g.* Zn-protein complexes); biodegradable polymers such as polyesters; and/or salt-forming counterions such as sodium.

The formulation herein may also contain more than one protein as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect the other protein. For example, it may be desirable to provide two or more antibodies which bind to the HER2 receptor or IgE in a single formulation. Furthermore, anti-HER2 and anti-VEGF antibodies may be combined in the one formulation. Such proteins are suitably present in combination in amounts that are effective for the purpose intended.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to, or following, lyophilization and reconstitution. Alternatively, sterility of the entire mixture may be accomplished by autoclaving the ingredients, except for protein, at about 120° C for about 30 minutes, for example.

After the protein, lyoprotectant and other optional components are mixed together, the formulation is lyophilized. Many different freeze-dryers are available for this purpose such as Hull50™ (Hull, USA) or GT20™ (Leybold-Heraeus, Germany) freeze-dryers. Freeze-drying is accomplished by freezing the formulation and subsequently subliming ice from the frozen content at a temperature suitable for primary drying. Under this condition, the product temperature is below the eutectic point or the collapse temperature of the formulation. Typically, the shelf temperature for the primary drying will range from about -30 to 25° C (provided the product remains frozen during primary drying) at a suitable pressure, ranging typically from about 50 to 250mTorr. The formulation, size and type of the container holding the sample (*e.g.*, glass vial) and the volume of liquid will mainly dictate the time required for drying, which can range from a few hours to several days (*e.g.* 40-60hrs). A secondary drying stage may be carried out at about 0-40° C, depending primarily on the type and size of container and the type of protein employed. However, it was found herein that a secondary drying step may not be necessary. For example, the shelf temperature throughout the entire water removal phase of lyophilization may be from about 15-30° C (*e.g.*, about 20° C). The time and pressure required for secondary drying will be that which produces a suitable lyophilized cake, dependent, *e.g.*, on the temperature and other parameters. The secondary drying time is dictated by the desired residual moisture level in the product and typically takes at least about 5 hours (*e.g.* 10-15 hours). The pressure may be the same as that employed during the primary drying step. Freeze-drying conditions can be varied depending on the formulation and vial size.

In some instances, it may be desirable to lyophilize the protein formulation in the container in which reconstitution of the protein is to be carried out in order to avoid a transfer step. The container in this instance may, for example, be a 3, 5, 10, 20, 50 or 100cc vial.

As a general proposition, lyophilization will result in a lyophilized formulation in which the moisture content thereof is less than about 5%, and preferably less than about 3%.

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C. **Reconstitution of the Lyophilized Formulation**

At the desired stage, typically when it is time to administer the protein to the patient, the lyophilized formulation may be reconstituted with a diluent such that the protein concentration in the reconstituted formulation is at least 50 mg/mL, for example from about 50 mg/mL to about 400 mg/mL, more preferably from about 80 mg/mL to about 300 mg/mL, and most preferably from about 90 mg/mL to about 150 mg/mL. Such high protein concentrations in the reconstituted formulation are considered to be particularly useful where subcutaneous delivery of the reconstituted formulation is intended. However, for other routes of administration, such as intravenous administration, lower concentrations of the protein in the reconstituted formulation may be desired (for example from about 5-50 mg/mL, or from about 10-40 mg/mL protein in the reconstituted formulation). In certain embodiments, the protein concentration in the reconstituted formulation is significantly higher than that in the pre-lyophilized formulation. For example, the protein concentration in the reconstituted formulation may be about 2-40 times, preferably 3-10 times and most preferably 3-6 times (*e.g.* at least three fold or at least four fold) that of the pre-lyophilized formulation.

Reconstitution generally takes place at a temperature of about 25°C to ensure complete hydration, although other temperatures may be employed as desired. The time required for reconstitution will depend, *e.g.*, on the type of diluent, amount of excipient(s) and protein. Exemplary diluents include sterile water, bacteriostatic water for injection (BWFI), a pH buffered solution (*e.g.* phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution. The diluent optionally contains a preservative. Exemplary preservatives have been described above, with aromatic alcohols such as benzyl or phenol alcohol being the preferred preservatives. The amount of preservative employed is determined by assessing different preservative concentrations for compatibility with the protein and preservative efficacy testing. For example, if the preservative is an aromatic alcohol (such as benzyl alcohol), it can be present in an amount from about 0.1-2.0% and preferably from about 0.5-1.5%, but most preferably about 1.0-1.2%.

Preferably, the reconstituted formulation has less than 6000 particles per vial which are ≥ 10 μm in size.

D. **Administration of the Reconstituted Formulation**

The reconstituted formulation is administered to a mammal in need of treatment with the protein, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerobrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes.

In preferred embodiments, the reconstituted formulation is administered to the mammal by subcutaneous (*i.e.* beneath the skin) administration. For such purposes, the formulation may be injected using a syringe. However, other devices for administration of the formulation are available such as injection devices (*e.g.* the Inject-ease™ and Genject™ devices); injector pens (such as the GenPen ™); needleless devices (*e.g.* MediJector™ and BioJector™); and subcutaneous patch delivery systems.

The appropriate dosage ("therapeutically effective amount") of the protein will depend, for example, on the condition to be treated, the severity and course of the condition, whether the protein is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the protein, the type of protein used, and the discretion of the attending physician. The protein is suitably administered to the patient at one time or over a series of treatments and may be administered to the patient at any time from

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diagnosis onwards. The protein may be administered as the sole treatment or in conjunction with other drugs or therapies useful in treating the condition in question.

Where the protein of choice is an antibody, from about 0.1-20 mg/kg is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques.

In the case of an anti-HER2 antibody, a therapeutically effective amount of the antibody may be administered to treat or prevent cancer characterized by overexpression of the HER2 receptor. It is contemplated that a reconstituted formulation of the anti-HER2 antibody may be used to treat breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon and/or bladder cancer. For example, the anti-HER2 antibody may be used to treat ductal carcinoma *in situ* (DCIS). Exemplary dosages of the anti-HER2 antibody are in the range 1-10 mg/kg by one or more separate administrations.

Uses for an anti-IgE formulation include the treatment or prophylaxis of IgE-mediated allergic diseases, parasitic infections, interstitial cystitis and asthma, for example. Depending on the disease or disorder to be treated, a therapeutically effective amount (*e.g.* from about 1-15 mg/kg) of the anti-IgE antibody is administered to the patient.

E. Articles of Manufacture

In another embodiment of the invention, an article of manufacture is provided which contains the lyophilized formulation of the present invention and provides instructions for its reconstitution and/or use. The article of manufacture comprises a container. Suitable containers include, for example, bottles, vials (*e.g.* dual chamber vials), syringes (such as dual chamber syringes) and test tubes. The container may be formed from a variety of materials such as glass or plastic. The container holds the lyophilized formulation and the label on, or associated with, the container may indicate directions for reconstitution and/or use. For example, the label may indicate that the lyophilized formulation is reconstituted to protein concentrations as described above. The label may further indicate that the formulation is useful or intended for subcutaneous administration. The container holding the formulation may be a multi-use vial, which allows for repeat administrations (*e.g.* from 2-6 administrations) of the reconstituted formulation. The article of manufacture may further comprise a second container comprising a suitable diluent (*e.g.* BWFI). Upon mixing of the diluent and the lyophilized formulation, the final protein concentration in the reconstituted formulation will generally be at least 50 mg/mL. The article of manufacture may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention. All literature citations are incorporated by reference.

EXAMPLE 1

ANTI-HER2 FORMULATION

Overexpression of the *HER2* proto-oncogene product ($p185^{HER2}$) has been associated with a variety of aggressive human malignancies. The murine monoclonal antibody known as muMAb4D5 is directed against the extracellular domain (ECD) of $p185^{HER2}$. The muMAb4D5 molecule has been humanized in an attempt to improve its clinical efficacy by reducing immunogenicity and allowing it to support human effector functions

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(see WO 92/22653). This example describes the development of a lyophilized formulation comprising full length humanized antibody huMAb4D5-8 described in WO 92/22653.

In the development of a lyophilized formulation, excipients and buffers are initially screened by measuring the stability of the protein after lyophilization and reconstitution. The lyophilized protein in each formulation is also subjected to accelerated stability studies to determine the potential stability of the protein over its shelf-life. These accelerated studies are usually performed at temperatures above the proposed storage conditions and the data are then used to estimate the activation energy for the degradation reactions assuming Arrhenius kinetics (Cleland *et al.*, *Critical Reviews in Therapeutic Drug Carrier Systems* 10(4): 307-377 (1993)). The activation energy is then used to calculate the expected shelf-life of the protein formulation at the proposed storage conditions.

In early screening studies, the stability of several lyophilized recombinant humanized anti-HER2 antibody (rhuMAb HER2) formulations was investigated after incubation at 5° C (proposed storage condition) and 40° C (accelerated stability condition). In the liquid state, rhuMAb HER2 was observed to degrade by deamidation (30Asn of light chain) and isoaspartate formation via a cyclic imide intermediate, succinimide (102Asp of heavy chain). The deamidation was minimized at pH 5.0 resulting in degradation primarily at the succinimide. At pH 6.0, slightly greater deamidation was observed in the liquid protein formulation. The lyophilized formulations were therefore studied with: (a) 5 or 10 mM succinate buffer, pH 5.0 or (b) 5 or 10 mM histidine buffer, pH 6.0. Both buffers contained the surfactant, polysorbate 20 (Tween 20™), which was employed to reduce the potential for aggregation of the reconstituted protein and minimize the formation of particulates after reconstitution. These buffers were used with and without various sugars. The protein was formulated in the buffer at 5.0, 21.0 or 25.0 mg/mL. These formulations were then lyophilized and assessed for protein stability after 2 weeks at 5° C and 40° C. In the lyophilizer, the vials were frozen at a shelf temperature of -55° C for approximately 5 hours followed by primary drying at a shelf temperature of 5° C and 150 mTorr for 30 hours, and drying to 1-2% residual moisture was achieved with secondary drying at a shelf temperature of 20° C for 10 hours. The major degradation route for this protein upon lyophilization was aggregation, and therefore the protein stability was assessed by native size exclusion chromatography to measure the recovery of intact native protein (% intact protein in Table 2 below).

The stabilizing effects of various lyoprotectant sugars on lyophilized protein was measured in 10 mM sodium succinate, pH 5.0 (Table 2). At high sugar concentrations (250-275 mM) and low protein concentration (5.0 mg/mL), trehalose and lactose stabilized the protein against aggregation for the lyophilized protein stored for 2 weeks at 40° C. However, lactose, a reducing sugar, was observed to react with the protein over longer term storage at 40° C. The formulations at 5.0 mg/mL protein containing either sorbitol or mannitol yielded aggregated protein after storage at 40° C for 2 weeks. At the higher protein concentration (21.0 mg/mL), formulations comprising mannitol, or mannitol in combination with sorbitol or glycine, contained aggregated protein after lyophilization and storage at both conditions. In contrast, trehalose and sucrose prevented aggregation at both storage conditions.

The 250 mM trehalose and 250 mM lactose formulations were assessed for long term stability. After 9 months at 40° C or 12 months at 5° C, there was no change in the % intact protein for the trehalose formulation. For the lactose formulation, the % intact protein remained constant (same as initial) after 3 months at 40° C or

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6 months at 25° C. The trehalose formulation could be stored at controlled room temperature (15-30° C) for 2 years without a significant change in % intact protein.

The 10 mM histidine, pH 6.0 formulation with mannitol contained less aggregated protein after storage at 40° C for 2 weeks than the 10 mM succinate formulation, pH 5.0 with mannitol. This result may be related to some stabilizing effect contributed by histidine alone. After storage at 40° C for 2 weeks, there was, however, significant aggregation for histidine alone or histidine/mannitol formulations. The addition of sucrose at an equal mass to mannitol (10 mg/mL of each) in the histidine formulation stabilized the protein against aggregation for both storage conditions. The use of glycine with mannitol did not improve the protein stability, while the sucrose/glycine formulation provided the same stability as the sucrose/mannitol formulation. These results further indicated that sucrose was useful for preventing aggregation of the lyophilized protein during storage.

TABLE 2

Composition Prior to Lyophilization		% Intact Protein[a]		
[Protein][b] (mg/mL)	Formulation	Liquid (5° C)	Lyophilized (2 wk, 5° C)	Lyophilized (2wk, 40° C)
	10 mM sodium succinate pH 5.0			
5.0	275 mM trehalose, 0.01% Tween 20™	98.9	99.1	98.9
5.0	275 mM lactose, 0.01% Tween 20™	96.8	96.5	96.6
5.0	275 mM sorbitol, 0.01% Tween 20™	99.4	99.3	95.4
5.0	250 mM mannitol, 0.01% Tween 20™	100.0	99.9	98.8
5.0	250 mM trehalose, 0.01% Tween 20™	100.0	99.9	100.0
5.0	250 mM lactose, 0.01% Tween 20™	100.0	100.0	100.0
21.0	250 mM trehalose, 0.2% Tween 20™	99.3	99.1	99.1
21.0	250 mM sucrose, 0.2% Tween 20™	99.6	99.6	99.7
21.0	250 mM mannitol, 0.01% Tween 20™	100.0	94.6	94.0
21.0	188 mM mannitol/63 mM sorbitol, 0.01% Tween 20™	99.8	98.6	96.5
21.0	250 mM mannitol/25 mM glycine, 0.01% Tween 20™	99.5	96.5	96.4
	10 mM histidine pH 6.0			
21.0	No sugar, 0.01% Tween 20™	100.0	99.9	98.9
21.0	54.9 mM mannitol, 0.01% Tween 20™	100.0	99.9	99.2
21.0	29.2 mM sucrose/266.4 mM glycine, 0.01% Tween 20™	100.0	100.0	99.6
21.0	54.9 mM mannitol/266.4 mM glycine, 0.01% Tween 20™	100.0	99.8	98.9

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Composition Prior to Lyophilization		% Intact Protein[a]		
[Protein][b] (mg/mL)	Formulation	Liquid (5° C)	Lyophilized (2 wk, 5° C)	Lyophilized (2wk, 40° C)
21.0	54.9 mM mannitol/29.2 mM sucrose, 0.01% Tween 20™	99.8	100.0	99.7

a. The fraction of intact protein was measured by native size exclusion HPLC and the peak area of the native protein relative to the total peak area including aggregates (TSK3000 SW XL column, TosoHaas, with a flow rate of 1.0 mL/min; elution with phosphate buffered saline; detection at 214 and 280 nm). The protein formulations were analyzed before lyophilization (liquid, 5° C) and after lyophilization and storage at 5° C or 40° C for 2 weeks.
b. Formulations containing 5 mg/mL protein were reconstituted with distilled water (20 mL, 5.0 mg/mL protein), and formulations containing 21 mg/mL protein were reconstituted with bacteriostatic water for injection (BWFI, 0.9% benzyl alcohol; 20 mL, 20 mg/mL protein).

The delivery of a high protein concentration is often required for subcutaneous administration due to the volume limitations (≤ 1.5 mL) and dosing requirements (≥100 mg). However, high protein concentrations (≥ 50 mg/mL) are often difficult to achieve in the manufacturing process since at high concentrations, the protein has a tendency to aggregate during processing and becomes difficult to manipulate (*e.g.* pump) and sterile filter. Alternatively, the lyophilization process may provide a method to allow concentration of the protein. For example, the protein is filled into vials at a volume (Vf) and then lyophilized. The lyophilized protein is then reconstituted with a smaller volume (Vr) of water or preservative (*e.g.* BWFI) than the original volume (*e.g.* Vr = 0.25Vf) resulting in a higher protein concentration in the reconstituted solution. This process also results in the concentration of the buffers and excipients. For subcutaneous administration, the solution is desirably isotonic.

The amount of trehalose in the lyophilized rhuMAb HER2 was reduced to produce an isotonic solution upon reconstitution to yield 100 mg/mL protein. The stabilizing effect of trehalose was determined as a function of concentration for 5 mM sodium succinate, pH 5.0 and 5 mM histidine, pH 6.0 at 25.0 mg/mL protein (Table 3). At trehalose concentrations from 60 to 200 mM, there was no significant aggregation after incubation of the lyophilized protein for 4 weeks at 40° C. These formulations were reconstituted with 20 mL of bacteriostatic water for injection (BWFI, USP, 0.9% benzyl alcohol). Reconstitution of the 50 mM trehalose formulation (5 mM sodium succinate) with 4 mL of BWFI (100 mg/mL protein) after incubation for 4 weeks at 40° C yielded a slight increase in aggregate formation. The preserved reconstituted formulations provided the advantage of multiple withdrawals from the same vial without sterility concerns. When sterile needles are used, these formulations would then allow for several doses from a single vial.

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TABLE 3

Composition Prior to Lyophilization		% Intact Protein[a]		
[Protein] (mg/mL)	Formulation	Liquid (5° C)	Lyophilized (4 wk, 5° C)	Lyophilized (4 wk, 40° C)
	5 mM sodium succinate pH 5.0			
25.0	50 mM trehalose, 0.01% Tween 20™ [b]	100.00	100.0	99.5
25.0	60 mM trehalose, 0.01% Tween 20™	100.0	100.0	99.9
25.0	60 mM trehalose, 0.01% Tween 20™	100.0	100.0	99.2
25.0	100 mM trehalose, 0.01% Tween 20™	100.0	100.0	99.7
25.0	150 mM trehalose, 0.01% Tween 20™	100.0	100.0	99.8
25.0	200 mM trehalose, 0.01% Tween 20™	100.0	100.0	100.0
	5 mM histidine pH 6.0			
25.0	38.4 mM mannitol/20.4 mM sucrose, 0.01% Tween 20™	100.0	100.0	99.3
25.0	38.4 mM mannitol/20.4 mM sucrose, 0.01% Tween 20™ [c]	100.0	100.0	99.4
25.0	60 mM trehalose, 0.01% Tween 20™ [d]	100.0	100.0	99.8
25.0	60 mM trehalose, 0.01% Tween 20™	100.0	100.0	99.4
25.0	100 mM trehalose, 0.01% Tween 20™	100.0	100.0	99.6
25.0	150 mM trehalose, 0.01% Tween 20™	100.0	100.0	100.0
25.0	200 mM trehalose, 0.01% Tween 20™	100.0	100.0	100.0

a. The fraction of intact protein was measured by native size exclusion HPLC and defined as the peak area of the native protein relative to the total peak area including aggregates (TSK3000 SW XL column, TosoHaas, with a flow rate of 1.0 mL/min; elution with phosphate buffered saline; detection at 214 and 280 nm). The protein formulations were analyzed before lyophilization (liquid, 5° C) and after lyophilization and storage at 5° C or 40° C for 4 weeks. Formulations were reconstituted with bacteriostatic water for injection (BWFI, USP, 0.9% w/w benzyl alcohol; 20 mL, 22 mg/mL protein).

b. Reconstituted with 4 mL of BWFI (0.9% benzyl alcohol) to yield 100 mg/mL protein.

c. Reconstituted with 4 mL of BWFI (1.1% benzyl alcohol) to yield 100 mg/mL protein.

d. Sample incubated for 2 weeks at 5° C or 40° C and then reconstituted with 20 mL of BWFI (0.9% benzyl alcohol) to yield 22 mg/mL protein.

Currently, rhuMAb HER2 is under investigation as a therapeutic for the treatment of breast cancer. The protein is dosed to patients at 2 mg/kg on a weekly basis. Since the average weight of these patients is 65 kg, the average weekly dose is 130 mg of rhuMAb HER2. For subcutaneous administration, injection volumes of 1.5 mL or less are well tolerated and, therefore, the protein concentration for a weekly subcutaneous administration of rhuMAb HER2 may be approximately 100 mg/mL (130 mg average dose/1.5 mL). As mentioned above, this high protein concentration is difficult to manufacture and maintain in a stable form. To achieve this high protein concentration, rhuMAb HER2 formulated in: (a) 5 mM sodium succinate, pH 5.0 or (b) 5 mM histidine, pH 6.0, was lyophilized at 25 mg/mL protein in 60 mM trehalose, 0.01% Tween 20™. The lyophilization was performed by filling 18 mL of the protein formulation into 50 cc vials. In the lyophilizer, the vials were frozen at a shelf

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temperature of -55° C for approximately 5 hours followed by primary drying at a shelf temperature of 5° C and 150 mTorr for 30 hours, and drying to 1-2% residual moisture was achieved with secondary drying at a shelf temperature of 20° C for 10 hours. Thermocouples placed in vials containing the placebo (formulation without protein) indicated that the product in the vials was maintained below -10° C throughout primary drying. Sequential stoppering studies during the lyophilization revealed that the residual moisture after primary drying was usually less than 10%.

The lyophilized protein was then reconstituted with either 4 or 20 mL of BWFI (0.9 or 1.1% benzyl alcohol) to yield concentrated protein solutions:

(a) 4 mL: 102 mg/mL rhuMAb HER2, 245 mM trehalose, 21 mM sodium succinate, pH 5.0 or 21 mM histidine, pH 6.0, 0.04% Tween 20™;

(b) 20 mL: 22 mg/mL rhuMAb HER2, 52 mM trehalose, 4 mM sodium succinate, pH 5.0 or 4 mM histidine, pH 6.0, 0.009% Tween 20™.

After storage of the lyophilized formulations for 4 weeks at 40° C and reconstitution to 22 mg/mL protein, the amount of aggregated protein appeared to increase slightly with decreasing trehalose concentration. The stability of the lyophilized protein was not affected by the volume of reconstitution. As shown in Figure 1, the amount of intact protein after incubation of the lyophilized protein at 40° C was the same for the 60 mM trehalose, 5 mM sodium succinate, pH 5.0, 0.01% Tween 20™ formulation reconstituted with either 4 or 20 mL of BWFI.

The results shown in Table 3 suggested that there may be a relationship between the trehalose concentration and the protein stability. To further assess this relationship, the formulations containing different concentrations of trehalose formulated in either sodium succinate or histidine were incubated for 91 days at 40° C. The stability was then measured as a function of the trehalose to protein molar ratio for each concentration of trehalose. As shown in Figure 2, the protein stability clearly decreased with decreasing trehalose concentration for both formulations. There was no apparent difference between the two buffers, succinate and histidine, in these formulations suggesting that the primary stabilizer under these conditions is trehalose. In addition, the observed decrease in intact protein for both these formulations would be acceptable even at the low trehalose concentration for a formulation that is stored at 2-8° C throughout its shelf-life. However, if controlled room temperature (30° C maxmimum temperature) stability is required, higher trehalose concentrations (≥ 600:1 trehalose:protein) may be needed depending on the stability specifications for the product (*i.e.* the specification for the amount of intact protein remaining after 2 years of storage). Typically, a controlled room temperature storage condition would require stability for 6 months at 40° C which is equivalent to storage at 30° C for 2 years.

As shown in Figure 3, the 250 mM trehalose formulation was unchanged after 6 months at 40° C while both the 60 mM trehalose formulations were less stable. The 60 mM trehalose formulations may then require refrigerated storage if the product specification at the end of its shelf-life is, for example, >98% intact protein by native size exclusion chromatography.

In the previous screening study, sucrose was also observed to prevent aggregation of rhuMAb HER2 after lyophilization and subsequent storage. To achieve isotonic solutions after reconstitution for subcutaneous administration (approximately four-fold concentration of formulation components and protein), the sucrose concentration must be reduced significantly. The equal mass concentration of sucrose and mannitol (bulking

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agent) used in the screening studies prevented aggregation of the protein. A lower concentration of sucrose and mannitol (equal mass concentrations) was chosen as a potential subcutaneous formulation of rhuMAb HER2. The protein solution (25 mg/mL protein, 5 mM histidine, pH 6.0, 38.4 mM (7 mg/mL) mannitol, 20.4 mM (7 mg/mL) sucrose, 0.01% Tween 20™) was lyophilized in the same manner as the 60 mM trehalose formulation except that the primary drying cycle was extended to 54 hours. After 4 weeks at 40°C, there was a slight increase in the amount of aggregates after reconstitution with 4.0 or 20.0 mL of BWFI (Table 3). The amount of aggregated protein was the same for reconstitution at 22 or 100 mg/mL protein (Figure 4). Like the 60 mM trehalose formulations, the mannitol/sucrose formulation yielded less intact protein over time at 40°C. The molar ratio of sucrose to protein for this formulation was 120 to 1, indicating that the mannitol/sucrose combination may be more effective than trehalose alone at the same molar ratio of stabilizing sugar (Figures 2 and 4).

In the previous examples, the stability of the lyophilized rhuMAb HER2 formulations was determined as a function of temperature. These studies demonstrated that the trehalose and mannitol/sucrose formulations prevented degradation of the protein in the lyophilized state at high temperatures (40°C). However, these experiments did not address the stability of the protein after reconstitution and storage. Once reconstituted with BWFI, the lyophilized rhuMAb HER2 formulations may be used for several administrations of the drug. In particular, the vial configuration (450 mg rhuMAb HER2) was designed to provide three doses to the average patient (130 mg rhuMAb HER2 per dose). Since the drug is dosed weekly, the vial may be stored at least three weeks after reconstitution. To assure that the rhuMAb HER2 remained stable after reconstitution, stability studies on the reconstituted rhuMAb HER2 formulations were performed at 5°C and 25°C.

For subcutaneous administration, the formulations were reconstituted to 100 mg/mL (4 mL BWFI). At this high protein concentration, the protein may be more susceptible to aggregation than the intravenous dosage form that was reconstituted to 22 mg/mL protein (20 mL BWFI). The four rhuMAb HER2 formulations from the previous example were assessed for aggregation (loss of intact protein). As shown in Tables 4 through 6, there was no difference in stability for formulations reconstituted at 22 and 100 mg/mL protein. Furthermore, these formulations maintained the protein completely intact for up to 90 days at 5 °C and 30 days at 25 °C, indicating that the reconstituted protein could be stored refrigerated for at least 90 days. Unlike the lyophilized protein stability in the previous example, the trehalose concentration in the formulation did not affect the protein stability (Table 7).

TABLE 4

Stability of the reconstituted formulations for rhuMAb HER2 lyophilized at 25 mg/mL protein in 5 mM sodium succinate, pH 5.0, 60 mM trehalose, 0.01% Tween 20™

Time (days)	% Intact Protein			
	22 mg/mL protein		100 mg/mL protein	
	5°C	25°C	5°C	25°C
0	99.9	99.9	99.7	99.7
14	ND	100.0	ND	100.0
30	100.0	100.0	100.0	100.0
91	99.8	ND	100	ND

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The samples were reconstituted with 4.0 or 20.0 mL of BWFI (1.1% or 0.9% benzyl alcohol), and then stored at 5°C or 25°C. The % intact protein was defined as the fraction of native peak area as measured by native size exclusion chromatography. ND = not determined.

TABLE 5

Stability of the reconstituted formulations for rhuMAb HER2 lyophilized at 25 mg/mL protein in 5 mM histidine, pH 6.0, 60 mM trehalose, 0.01% Tween 20™

Time (days)	% Intact Protein			
	22 mg/mL protein		100 mg/mL protein	
	5°C	25°C	5°C	25°C
0	100.0	100.0	100.0	100.0
14	ND	100.0	ND	100.0
31	99.3	99.7	100.0	100.0
61	100.0	ND	ND	ND

The samples were reconstituted with 4.0 or 20.0 mL of BWFI (1.1% or 0.9% benzyl alcohol), and then stored at 5°C or 25 °C. The % intact protein was defined as the fraction of native peak area as measured by native size exclusion chromatography. ND = not determined.

TABLE 6

Stability of the reconstituted formulations for rhuMAb HER2 lyophilized at 25 mg/mL protein in 5 mM histidine, pH 6.0, 38.4 mM mannitol, 20.4 mM sucrose, 0.01% Tween 20™

Time (days)	% Intact Protein			
	22 mg/mL protein		100 mg/mL protein	
	5°C	25°C	5°C	25°C
0	99.7	99.7	99.8	99.8
14	ND	100.0	ND	99.8
31	100.0	100.0	100.0	100.0
92	100.0	ND	100.0	ND

The samples were reconstituted with 4.0 or 20.0 mL of BWFI (1.1% or 0.9% benzyl alcohol), and then stored at 5°C or 25 °C. The % intact protein was defined as the fraction of native peak area as measured by native size exclusion chromatography. ND = not determined.

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TABLE 7

Stability of the reconstituted formulations for rhuMAb HER2 lyophilized at 21 mg/mL protein in 10 mM sodium succinate, pH 5.0, 250 mM trehalose, 0.2% Tween 20™

Time (days)	% Intact Protein 21 mg/mL protein	
	5°C	25°C
0	99.8	99.8
14	ND	100.0
31	99.9	99.4
92	99.8	ND

The samples were reconstituted with 20.0 mL of BWFI (0.9% benzyl alcohol), and then stored at 5°C or 25°C. The % intact protein was defined as the fraction of native peak area as measured by native size exclusion chromatography. ND = not determined.

As mentioned previously, the major degradation route for rhuMAb HER2 in aqueous solutions is deamidation or succinimide formation. The loss of native protein due to deamidation or succinimide formation was assessed for the four reconstituted rhuMAb HER2 formulations.

Analysis of rhuMAb HER2 deamidation and succinimide formation was performed using cation exchange chromatography. A Bakerbond Wide-Pore Carboxy Sulfon (CSX) column (4.6 x 250 mm) was operated at a flow rate of 1 mL/min. The mobile phase buffers were (A) 0.02 M sodium phosphate, pH 6.9, and (B) 0.02 M sodium phosphate, pH 6.9, 0.2 M NaCl. The chromatography was then performed at 40°C as follows:

TABLE 8

Time (min)	% Buffer B
0	10
55	45
57	100
62	100
62.1	10
63	10

Peak elution was monitored at 214 nm and 75 µg of protein was loaded for each analysis.

Again, there were no differences in stability of the formulations reconstituted at 22 and 100 mg/mL protein (Figures 5 through 7). The protein degradation was more rapid at 25°C than 5°C for each formulation, and the rate of degradation was comparable for all the formulations stored at 5°C. The formulations containing histidine underwent a slightly greater rate of degradation at 25°C than the succinate formulations. The amount of trehalose in the formulation did not affect the degradation rate at either temperature (Figures 5 and 8). These

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results indicated that these four formulations provide an acceptable rate of degradation under refrigerated storage conditions (5° C) for the intended period of use (30 days after reconstitution with BWFI).

Multi-use formulations should pass preservative efficacy testing as described by the US Pharmacopeia (USP) for use in the United States. The rhuMAb HER2 lyophilized formulation consisting of 25 mg/mL protein, 5 mM histidine, pH 6.0, 60 mM trehalose, 0.01% Tween 20™ was reconstituted with 20 mL of benzyl alcohol at concentrations between 0.9 and 1.5% w/w. For concentrations at or above 1.3% w/w, the reconstituted solution became cloudy after overnight incubation at room temperature (~25 °C). Reconstitution with the standard BWFI solution (0.9% benzyl alcohol) resulted in a solution that did not consistently pass the preservative challenge tests. However, reconstitution with 1.0 or 1.1% benzyl alcohol was both compatible with the formulation and passed the preservative challenge testing. The manufacturer's specifications for the solution required a range of ± 10%, and therefore, the lyophilized formulations are reconstituted with 1.1% benzyl alcohol (1.1 ± 0.1%).

A single step lyophilization cycle for the rhuMAb HER2 formulation was developed . In the single step lyophilization cycle, rhuMAb HER2 at 25 mg/mL, 60 mM trehalose, 5 mM histidine pH 6 and 0.01% polysorbate 20 was lyophilized at a shelf temperature of 20° C. and a pressure of 150 mTorr. After 47 hours, the residual moisture content of the lyophilized cake was less than 5%. This lyophilization cycle is considered to be useful in that it simplifies the manufacturing process, by eliminating the secondary drying step.

EXAMPLE 2

ANTI-IgE FORMULATION

IgE antibodies bind to specific high-affinity receptors on mast cells, leading to mast cell degranulation and release of mediators, such as histamine, which produce symptoms associated with allergy. Hence, anti-IgE antibodies that block binding of IgE to its high-affinity receptor are of potential therapeutic value in the treatment of allergy. These antibodies must also not bind to IgE once it is bound to the receptor because this would trigger histamine release. This example describes the development of a lyophilized formulation comprising full length humanized anti-IgE antibody MaE11 described in Presta *et al. J. Immunology,* 151: 2623-2632 (1993).

Materials: Highly purified rhuMAb E25 (recombinant humanized anti-IgE antibody MaE11) which did not contain Tween 20™ was used in the formulations described below. Spectra/Por 7 dialysis membranes were purchased from Spectrum (Los Angeles, CA). All other reagents used in this study were obtained from commercial sources and were of analytical grade. Formulation buffers and chromatography mobile phase were prepared by mixing the appropriate amount of buffer and salt with Milli-Q water in a volumetric flask.

Formulation: E25 S Sepharose pool was dialyzed into formulation buffers as specified. Dialysis was accomplished by a minimum of 4 x 2L buffer exchanges over a 48 hour period at 2-8° C. Following dialysis, lyoprotectant was added at a isotonic concentration to some of the formulations as required. Protein concentration following dialysis was determined by UV spectroscopy using a molar absorptivity of 1.60. The dialyzed protein was diluted to the predetermined formulation concentration with an appropriate formulation buffer, sterile filtered using a 0.22 μm Millex-GV filter (Millipore) and dispensed into pre-washed and autoclaved glass vials. The vials were fitted with siliconized teflon lyophilization stoppers and lyophilized using the following conditions: the E25 formulation was frozen to -55° C at 80° C/hour and the vial content was kept frozen for 4 hours. The shelf temperature was ramped to 25° C at 10° C/hour for primary drying. Primary

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drying was carried out at 25° C, 50 μ chamber vacuum pressure for 39 hours such that the residual moisture of the lyophilized cake was 1-2%. Following lyophilization, a vial of each formulation was removed for t=0 analysis and the remaining vials were held at various temperatures which include -70° C, 2-8° C, 25° C, 30° C (controlled room temperature) 40° C and 50° C.

Chromatography: Native size exclusion chromatography was carried out on a Bio-Rad Bio-Select™ SEC 250-5 column (300 x 7.8 mm). The column was equilibrated and ran in PBS at a flow rate of 0.5 mL/min using a Hewlett Packard 1090L HPLC equipped with a diode array detector. Molecular weight standards (Bio-Rad, Inc.) consisting of thyroglobulin (670 kd), gamma-globulin (158 kd), ovalbumin (44 kd), and cyanocobalamin (1.35 kd) were used to calibrate the column. The sample load was 25 μg and protein was detected by monitoring the UV absorption at 214 nm using Turbochrom 3 software (PE Nelson, Inc).

Hydrophobic Interaction Chromatography: $F(ab')_2$ fragments of the E25 antibody were chromatographed using a TosoHaas Butyl-NPR column (3.5 x 4.6 mm) and a Hewlett Packard 1090L HPLC equipped with a diode array detector. Elution buffer A was: 20 mM Tris, 2 M ammonium sulfate, 20% (v/v) glycerol, pH 8.0 while elution buffer B was: 20 mM Tris, 20% (v/v) glycerol, pH 8.0. The column was equilibrated with 10% elution buffer B at a flow rate of 1.0 mL/min for a minimum of 20 minutes. The sample load was 5 μg and protein was detected by monitoring the UV absorption at 214 nm using Turbochrom 3 data acquisition software (PE Nelson, Inc). Following injection of the sample, the column was maintained at 10% buffer B for 1 minute followed by a linear gradient of from 10% to 62% buffer B in 20 minutes. The column was washed with 100% buffer B for 5 minutes and re-equilibrated with 10% buffer B for a minimum of 20 minutes between successive sample injections.

Antibody Binding Activity: IgE receptor binding inhibition assay (IE25:2) was carried out as described in Presta *et al.*, *supra*, on samples diluted to 20 μg/mL and 30 μg/mL in assay diluent (phosphate buffered saline, 0.5% BSA, 0.05% polysorbate 20, 0.01% Thimerosol). Each dilution was then assayed in triplicate and the results were multiplied by an appropriate dilution factor to yield an active concentration. The results from 6 assays were averaged. The assay measures the ability of rhuMAb E25 to competitively bind to IgE and thereby prevent IgE from binding to its high affinity receptor which is immobilized to an ELISA plate. The results are divided by the antibody concentration as determined by UV absorption spectroscopy and reported as a specific activity. Previous experiments have shown that this assay is stability indicating.

Particulate Assay: Reconstituted vials of lyophilized rhuMAb E25 were pooled to achieve a volume of approximately 7 mL. A count of the number of particles of size ranging from 2 to 80 μm present in 1 mL of sample was determined using a Hiac/Royco model 8000 counter. The counter was first washed with 1 mL of sample three times followed by the measurement of 1 mL of sample in triplicate. The instrument determines the number of particles per mL that are equal to or greater than 10 μm and the number of particles per mL that are equal to or greater than 25 μm.

The first step in the development of a formulation for the anti-IgE antibody was to determine a suitable buffer and pH for lyophilization and storage of the product. Antibody at a concentration of 5.0 mg/mL was formulated into 10 mM succinate buffers ranging from pH 5.0 to pH 6.5 and into sodium phosphate, potassium phosphate and histidine buffers at pH 7.0. Figure 9 shows increased antibody aggregate was observed in the higher pH formulations both before and after lyophilization. An exception was the histidine formulation at pH

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7, where no increase in aggregate was observed upon storage at 2-8° C. Figure 10 shows rhuMAb E25 lyophilized in 5 mM histidine buffer at both pH 6 and pH 7 and stored for 1 year at 2-8° C, 25° C, and 40° C. At each assay time point and storage temperature the pH 6 formulation had less aggregate than the antibody formulated at pH 7. These results show histidine at pH 6 is a particularly useful buffer system for preventing aggregation of the antibody.

To facilitate screening of lyoprotectants, the anti-IgE antibody was formulated into sodium succinate at pH 5 with or without a lyoprotectant. Potential lyoprotectants, added at isotonic concentrations, were grouped into 3 categories:

(a) non-reducing monosaccharide (*i.e.* mannitol);

(b) reducing disaccharides (*i.e.* lactose and maltose); and

(c) non-reducing disaccharides (*i.e.* trehalose and sucrose).

Aggregation of the formulations following storage at 2-8° C and 40° C for one year is shown in Figures 11 and 12. With storage at 2-8° C, the monosaccharide formulation (mannitol) aggregated at a rate similar to the buffer control, while formulations containing the disaccharides were equally effective in controlling aggregation (Figure 11). The results following storage at 40° C where similar with the exception of the sucrose formulation which rapidly aggregated (which correlated with a browning of the freeze-dried cake (Figure 12)). This was later shown to be caused by degradation of sucrose following storage at both acidic pH and high temperature.

Hydrophobic interaction chromatography of the antibody formulated in histidine buffer at pH 6 with lactose shows the antibody is altered following storage for 6 months at 40° C (Figure 13). The chromatography peaks are broadened and the retention time decreases. These changes are not observed with the buffer control and sucrose formulations stored under similar conditions as shown in Figures 14 and 15, respectively. Furthermore, isoelectric focusing showed an acidic shift in the pI of the antibody formulated in lactose and stored at 25° C and 40° C. This indicates that reducing sugars are not suitable as lyoprotectants for the antibody.

Aggregation of lyophilized formulations of anti-IgE at a concentration of 20 mg/mL in 5 mM histidine buffer at pH 6 with various concentrations of sucrose and trehalose following storage for 12 weeks at 50° C is shown in Figure 16. Both sugars have a similar protective effect on aggregation when the sugar concentration is greater than 500 moles of sugar per mole of antibody. From these results, isotonic and hypertonic formulations of both sucrose and trehalose were identified for further development. The formulations are designed to be filled prior to lyophilization at a relatively low concentration of antibody and the lyophilized product is reconstituted with less volume than was filled with bacteriostatic water for injection (BWFI) comprising 0.9% benzyl alcohol. This allows the concentration of the antibody immediately prior to subcutaneous delivery and includes a preservative for a potential multi-use formulation while avoiding interactions between the protein and preservative upon long-term storage.

Isotonic formulation: Anti-IgE at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM. This formulation is reconstituted with BWFI (0.9% benzyl alcohol) at a volume which is four times less than was filled. This results in a 100 mg/mL of antibody in 20 mM histidine at pH 6 with an isotonic sugar concentration of 340 mM.

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Hypertonic formulation: Anti-IgE at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM. This formulation is reconstituted with BWFI (0.9% benzyl alcohol) at a volume which is four times less than was filled. This results in a 100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM.

Comparisons of the antibody aggregation following storage of the isotonic and hypertonic formulations for up to 36 weeks are shown in Figures 17 to 19. No change in aggregation is observed in either the hypertonic or isotonic formulations with storage at 2-8° C (Figure 17). With storage at controlled room temperature (30° C) increased aggregation is not observed in the hypertonic formulations while an increase in aggregate of from 1 to 2% occurs in the isotonic formulations (Figure 18). Finally, following storage at 50° C a minimal increase in aggregate is observed with the hypertonic formulations, a 4% increase in aggregate occurs with the isotonic trehalose formulation and a 12% increase in aggregate occurs with the isotonic sucrose formulation (Figure 19). These results show the isotonic formulation contains the minimum amount of sugar necessary to maintain the stability of the antibody with storage at a temperature up to 30° C.

The binding activity of the anti-IgE in the isotonic and hypertonic formulations was measured in an IgE receptor inhibition assay. It was discovered that the binding activity of the isotonic and hypertonic sucrose and trehalose formulations was essentially unchanged following storage at -70° C, 2-8° C, 30° C and 50° C for up to 36 weeks.

Lyophilized formulations of proteins are known to contain insoluble aggregates or particulates (Cleland *et al., Critical Reviews in Therapeutic Drug Carrier Systems*, 10 (4):307-377 (1993)). Accordingly, a particulate assay of antibody lyophilized at a concentration of 25 mg/mL in 5 mM histidine, pH 6 with the addition of 85 mM and 161 mM sucrose and trehalose was performed. Polysorbate 20 was added to the formulations at a concentration of 0.005%, 0.01%, and 0.02%. Samples were lyophilized and assayed following reconstitution to 100 mg/mL antibody in 20 mM histidine, pH 6 with 340 mM and 644 mM sugar. The polysorbate 20 concentration following reconstitution was 0.02%, 0.04%, and 0.08%.

Table 9 below shows the number of particles of size equal to or greater than 10 μm and equal to or greater than 25 μm from the isotonic and hypertonic sucrose and trehalose formulations. Polysorbate 20 was added to the formulations at concentrations of 0.005%, 0.01%, and 0.02% prior to lyophilization. The results show that the addition of Tween™ to the formulation significantly reduces the number of particles in each size range tested. The US Pharmacopeia (USP) specification for small volume injections are not more than 6,000 particles of greater than or equal to 10 μm and not more than 600 particles of greater than or equal to 25 μm per container (Cleland *et al., supra*). With the addition of polysorbate 20, both the hypertonic and isotonic formulations pass this specification.

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TABLE 9

Formulation	Polysorbate 20	Particles per mL	
		≥ 10 µm	≥ 25 µM
Isotonic Sucrose	None	16,122	28
	0.005%	173	2
	0.01%	224	5
	0.02%	303	6
Hypertonic Sucrose	None	14,220	84
	0.005%	73	6
	0.01%	51	0
	0.02%		6
Isotonic Trehalose	None	33,407	24
	0.005%	569	4
	0.01%	991	16
	0.02%	605	9
Hypertonic Trehalose	None	24,967	28
	0.005%	310	11
	0.01%	209	6
	0.02%	344	6

One formulation developed for the anti-IgE antibody (*i.e.* 143 mg vial isotonic formulation of rhuMAb E25) which is considered to be useful for subcutaneous delivery of this antibody is shown in Table 10 below. A 10 cc vial is filled with 5.7 mL of rhuMAb E25 at a concentration of 25 mg/mL formulated in 5 mM histidine at pH 6.0 with 0.01% polysorbate 20. Sucrose is added as a lyoprotectant at a concentration of 85 mM which corresponds to a molar ratio of sugar to antibody of 500 to 1. The vial is lyophilized and reconstituted with 0.9% benzyl alcohol to one quarter of the volume of the fill or 1.2 mL. The final concentration of components in the formulation is increased four fold to 100 mg/mL rhuMAb E25 in 20 mM histidine at pH 6 with 0.04% polysorbate 20 and 340 mM sucrose (isotonic) and 0.9% benzyl alcohol. The formulation contains histidine buffer at pH 6 because of its demonstrated protective effect on antibody aggregation. Sucrose was added as the lyoprotectant because of previous use in the pharmaceutical industry. The concentration of sugar was chosen to result in an isotonic formulation upon reconstitution. Finally, polysorbate 20 is added to prevent the formation of insoluble aggregates.

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TABLE 10

Pre-lyophilized Formulation (Fill 5.7 mL into 10 cc vial)	Reconstituted Formulation (1.2 mL 0.9% Benzyl Alcohol)
25 mg/mL rhuMAb E25	100 mg/mL rhuMAb E25
5 mM Histidine, pH 6.0	20 mM Histidine, pH 6.0
85 mM Sucrose	340 mM Sucrose
0.01% Polysorbate 20	0.04% Polysorbate 20
-	0.9% Benzyl Alcohol

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WHAT IS CLAIMED IS:

1. A stable isotonic reconstituted formulation comprising a protein in an amount of at least about 50 mg/mL and a diluent, which reconstituted formulation has been prepared from a lyophilized mixture of a protein and a lyoprotectant, wherein the protein concentration in the reconstituted formulation is about 2-40 times greater than the protein concentration in the mixture before lyophilization.

2. The formulation of claim 1 wherein the lyoprotectant is sucrose or trechalose.

3. The formulation of claim 1 which further comprises a buffer.

4. The formulation of claim 3 wherein the buffer is histidine or succinate.

5. The formulation of claim 1 which further comprises a surfactant.

6. A stable reconstituted formulation comprising an antibody in an amount of at least about 50 mg/mL and a diluent, which reconstituted formulation has been prepared from a lyophilized mixture of an antibody and a lyoprotectant, wherein the antibody concentration in the reconstituted formulation is about 2-40 times greater than the antibody concentration in the mixture before lyophilization.

7. The formulation of claim 6 wherein the antibody is an anti-IgE antibody or anti-HER2 antibody.

8. The formulation of claim 6 which is isotonic.

9. A method for preparing a stable isotonic reconstituted formulation comprising reconstituting a lyophilized mixture of a protein and a lyoprotectant in a diluent such that the protein concentration in the reconstituted formulation is at least 50 mg/mL, wherein the protein concentration in the reconstituted formulation is about 2-40 times greater than the protein concentration in the mixture before lyophilization.

10. A method for preparing a formulation comprising the steps of:

(a) lyophilizing a mixture of a protein and a lyoprotectant; and

(b) reconstituting the lyophilized mixture of step (a) in a diluent such that the reconstituted formulation is isotonic and stable and has a protein concentration of at least about 50 mg/mL.

11. The method of claim 10 wherein the protein concentration in the reconstituted formulation is from about 80 mg/mL to about 300 mg/mL.

12. The method of claim 10 wherein the protein concentration in the reconstituted formulation is about 2-40 times greater than the protein concentration in the mixture before lyophilization.

13. The method of claim 10 wherein lyophilization is performed at a shelf temperature maintained at about 15-30°C throughout the entire lyophilization process.

14. An article of manufacture comprising:

(a) a container which holds a lyophilized mixture of a protein and a lyoprotectant; and

(b) instructions for reconstituting the lyophilized mixture with a diluent to a protein concentration in the reconstituted formulation of at least about 50 mg/mL.

15. The article of manufacture of claim 14 further comprising a second container which holds a diluent.

16. The article of manufacture of claim 15 wherein the diluent is bacteriostatic water for injection (BWFI) comprising an aromatic alcohol.

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17. A formulation comprising a lyophilized mixture of a lyoprotectant and an antibody, wherein the molar ratio of lyoprotectant:antibody is about 100-1500 mole lyoprotectant:1 mole antibody.

18. Use of the formulation of claim 1 in the preparation of a medicament for treating a mammal which has a disorder requiring treatment with the protein in the formulation.

19. Use as in claim 18 wherein the formulation is for subcutaneous administration.

20. A formulation comprising anti-HER2 antibody in amount from about 5-40 mg/mL, sucrose or trehalose in an amount from about 10-100 mM, a buffer and a surfactant.

21. The formulation of claim 20 further comprising a bulking agent.

22. The formulation of claim 20 which is lyophilized and stable at 30° C for at least 6 months.

23. The formulation of claim 20 which is reconstituted with a diluent such that the anti-HER2 antibody concentration in the reconstituted formulation is from about 10-30 mg/mL, wherein the reconstituted formulation is stable at 2-8° C for at least about 30 days.

24. A formulation comprising anti-IgE antibody in amount from about 5-40 mg/mL, sucrose or trehalose in an amount from about 80-300 mM, a buffer and a surfactant.

25. The formulation of claim 24 which is lyophilized and stable at about 30° C for at least 1 year.

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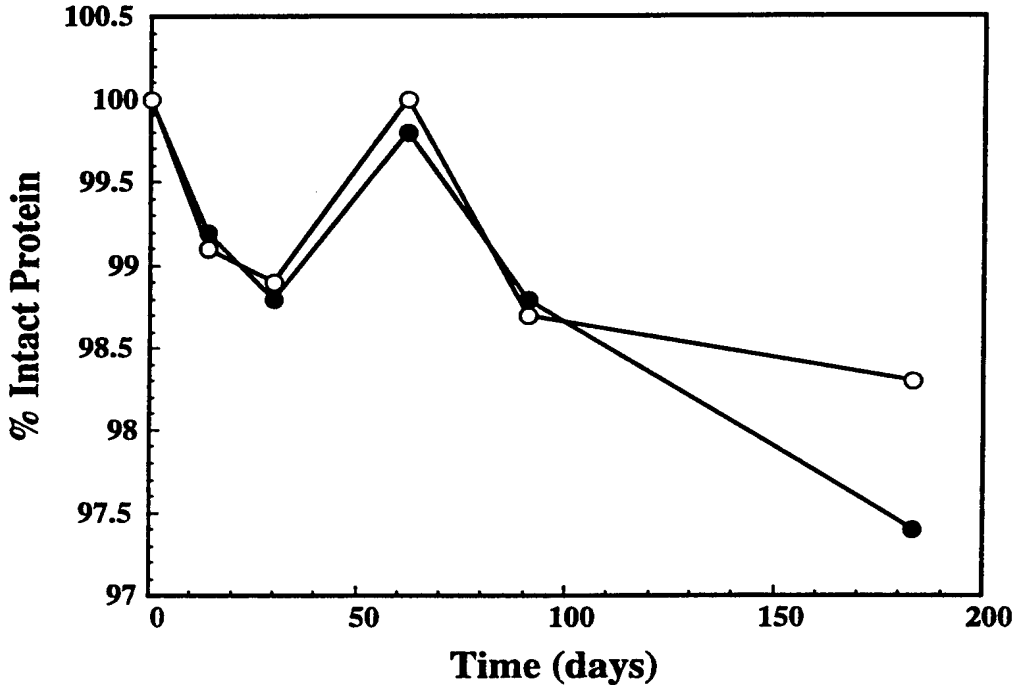


FIG. 1

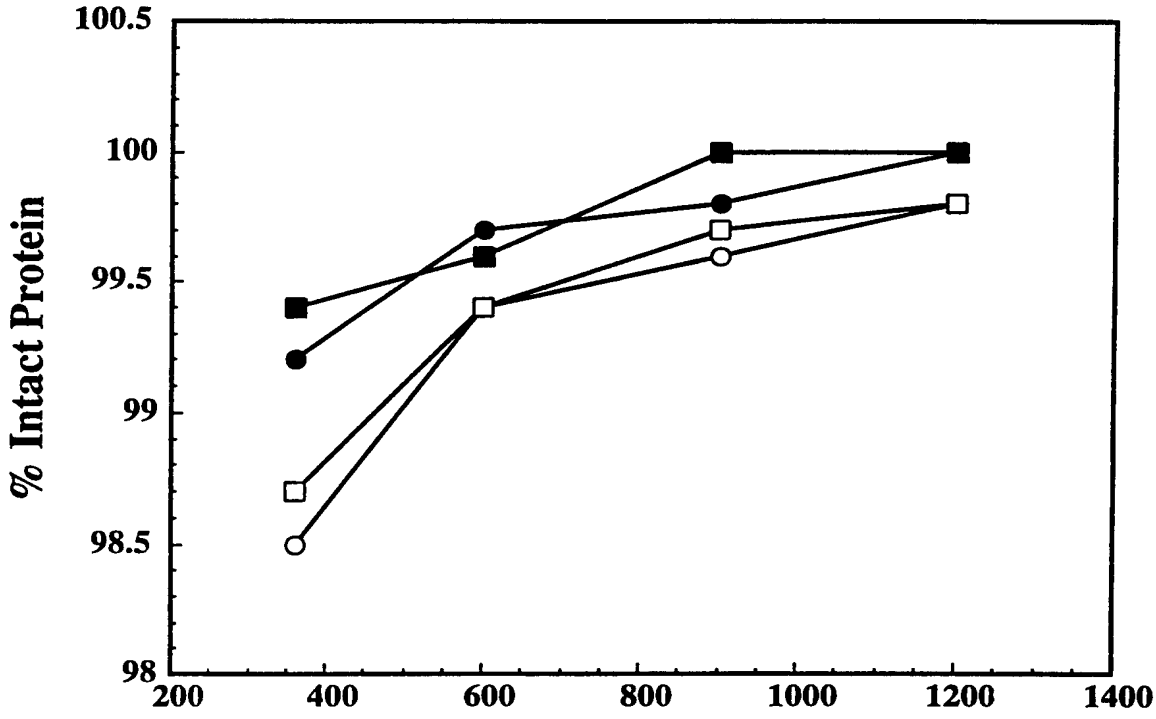


FIG. 2

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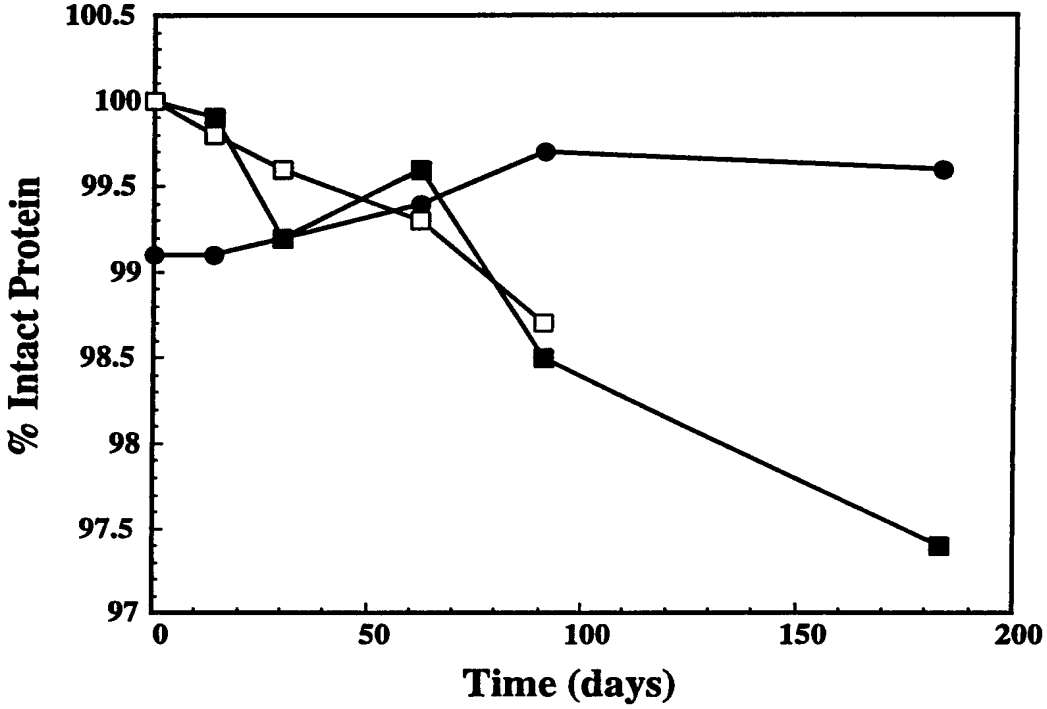


FIG. 3

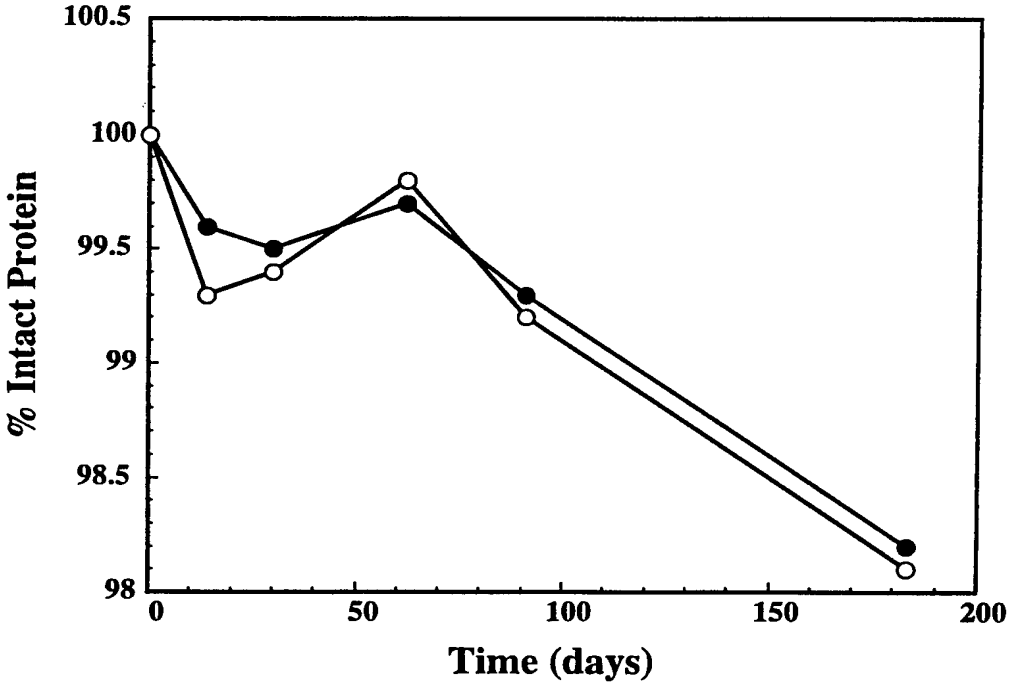


FIG. 4

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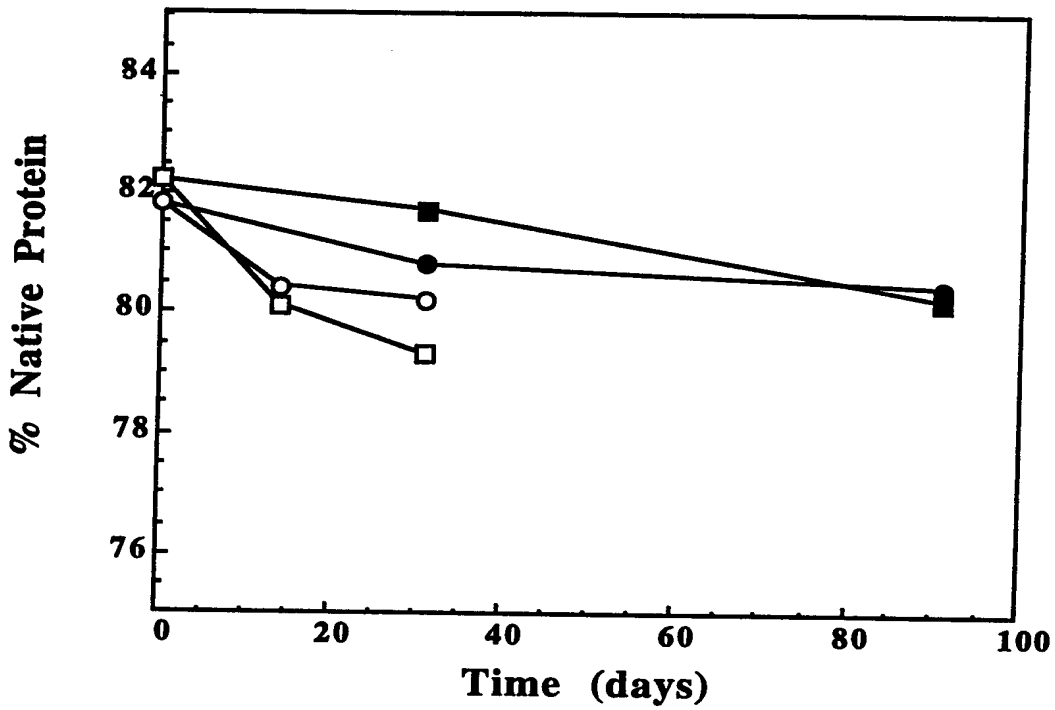


FIG. 5

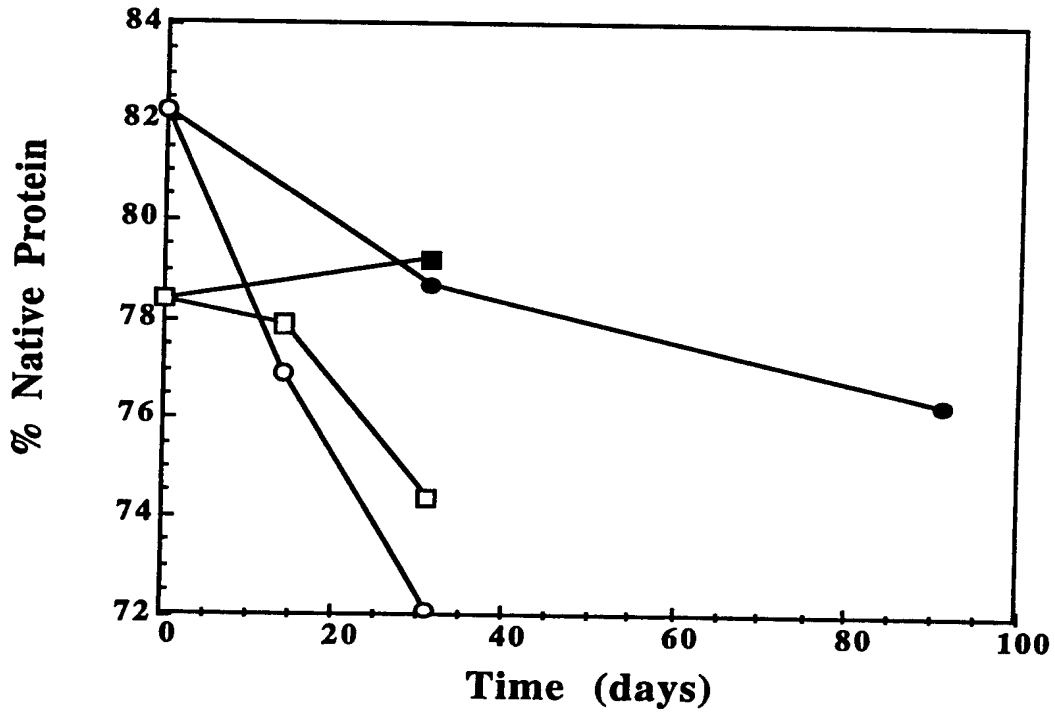


FIG. 6

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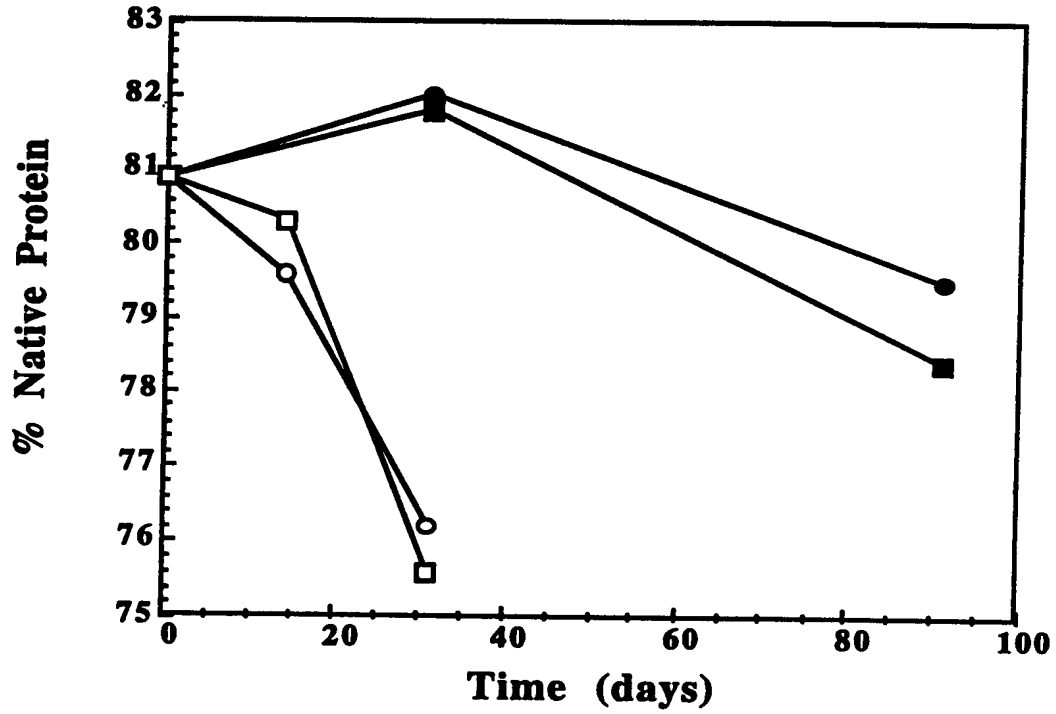


FIG. 7

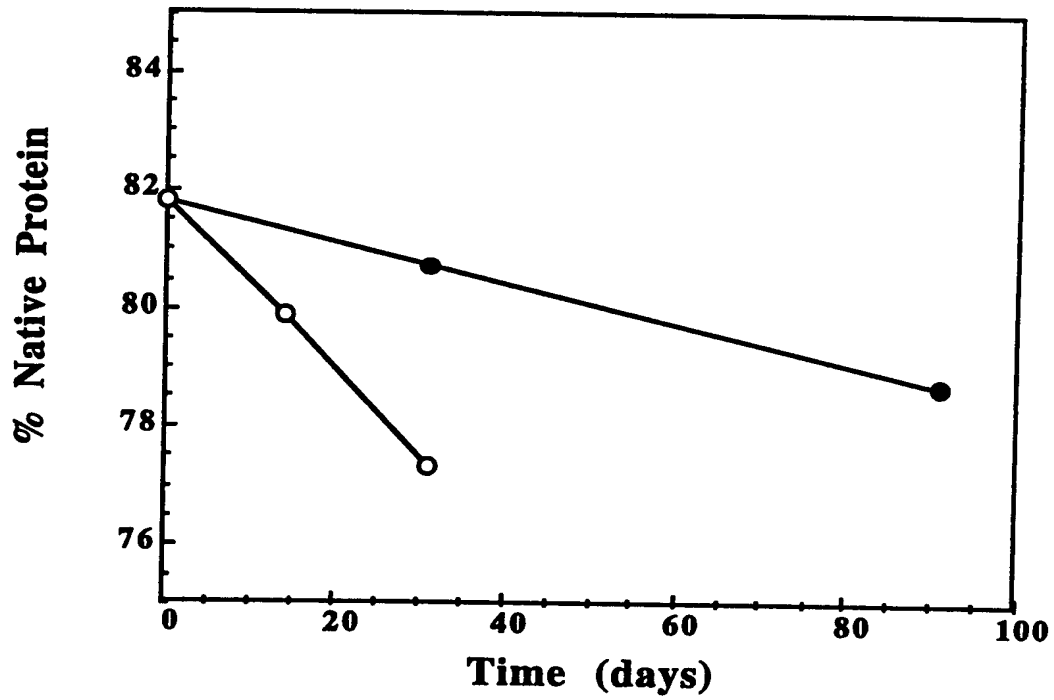


FIG. 8

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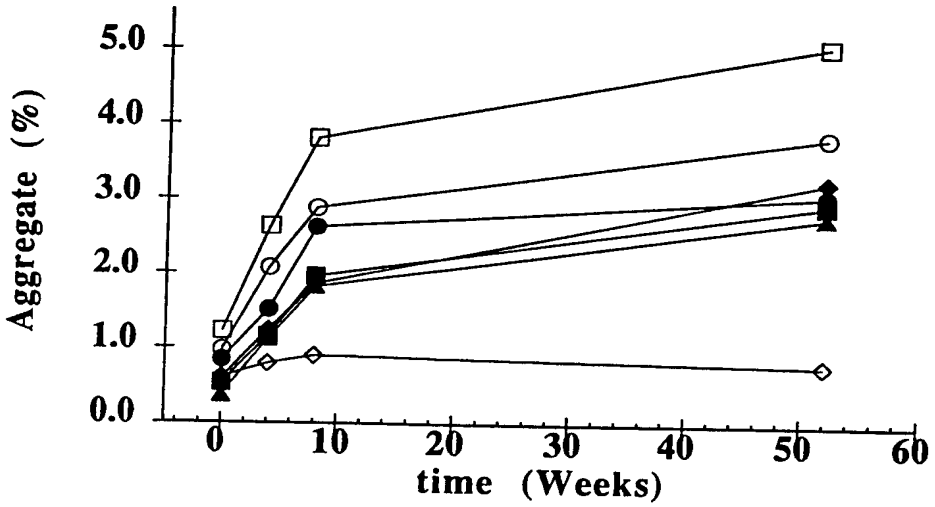


FIG. 9

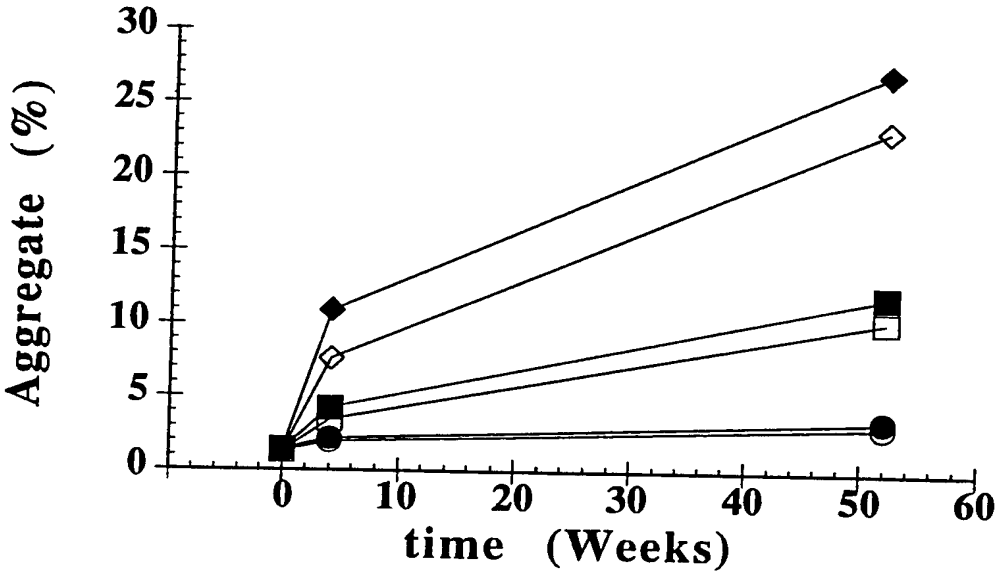


FIG. 10

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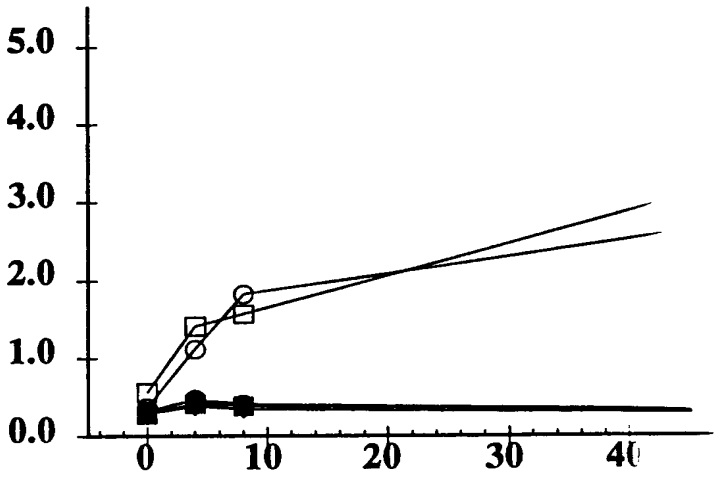


FIG. 11

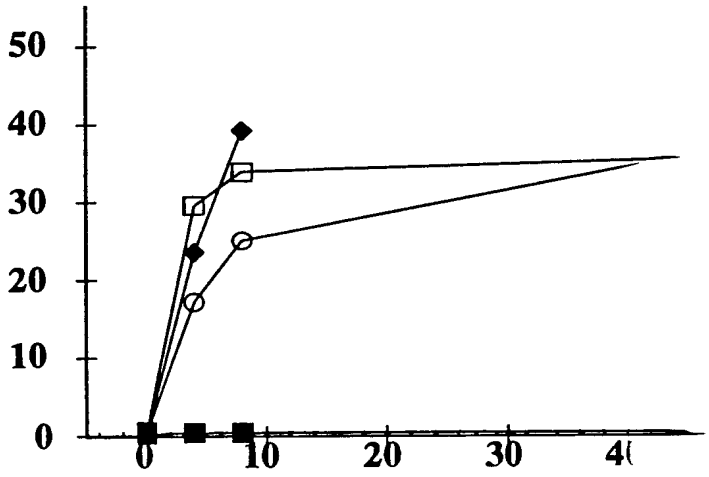


FIG. 12

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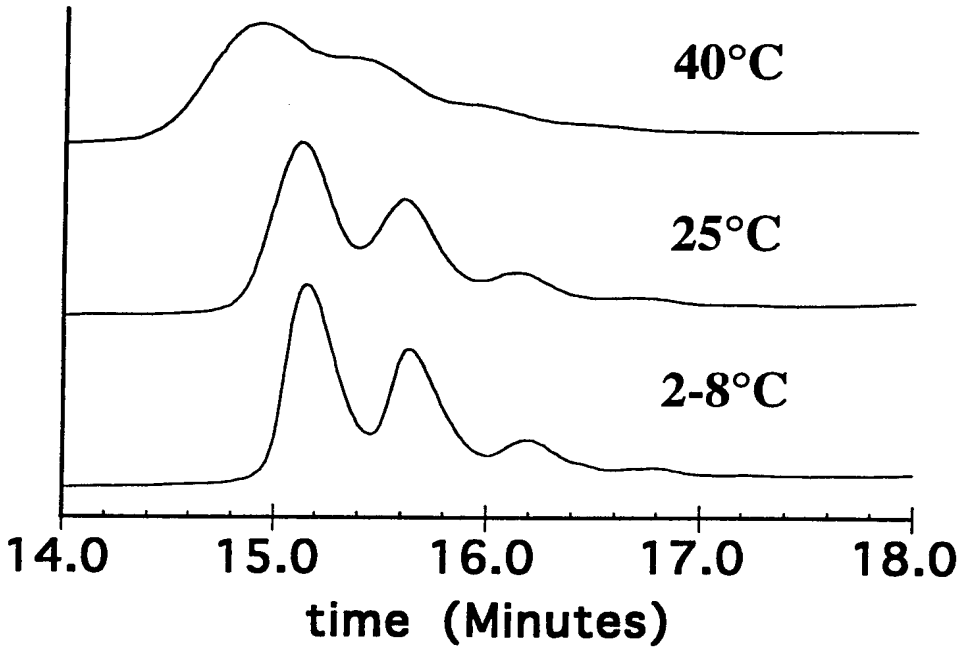


FIG. 13

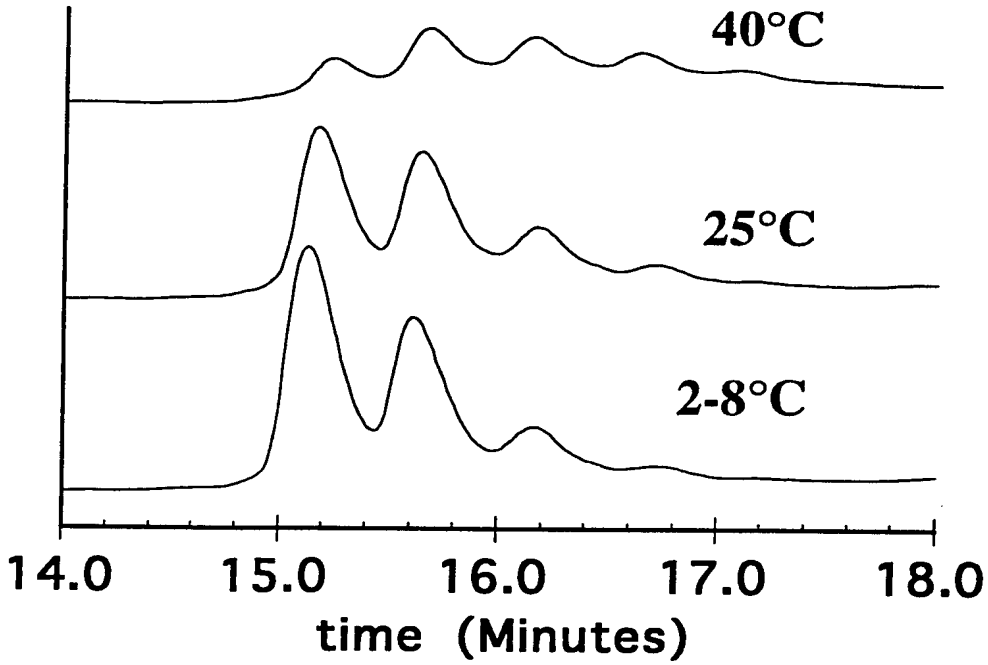


FIG. 14

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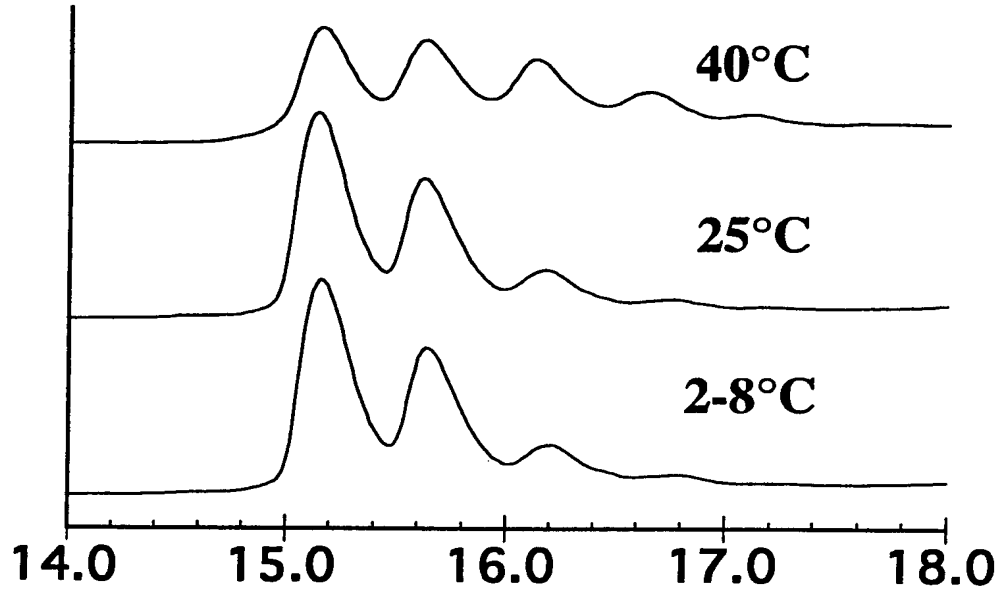


FIG. 15

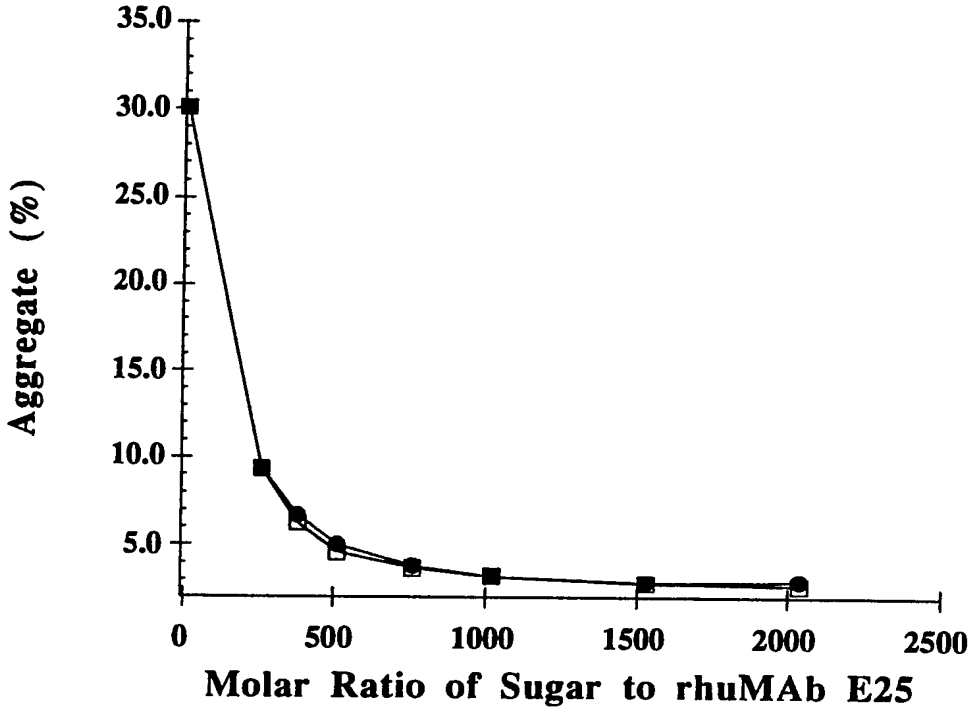


FIG. 16

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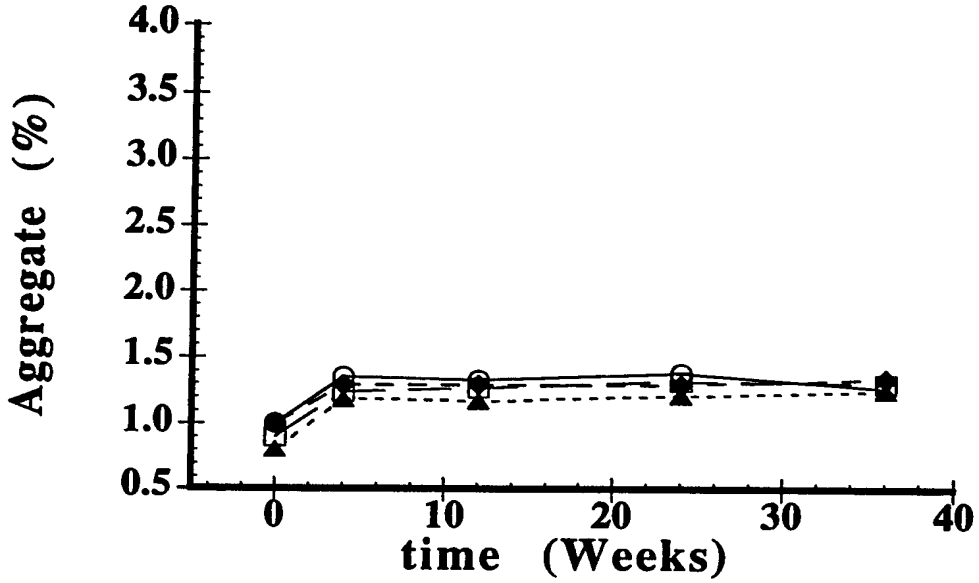


FIG. 17

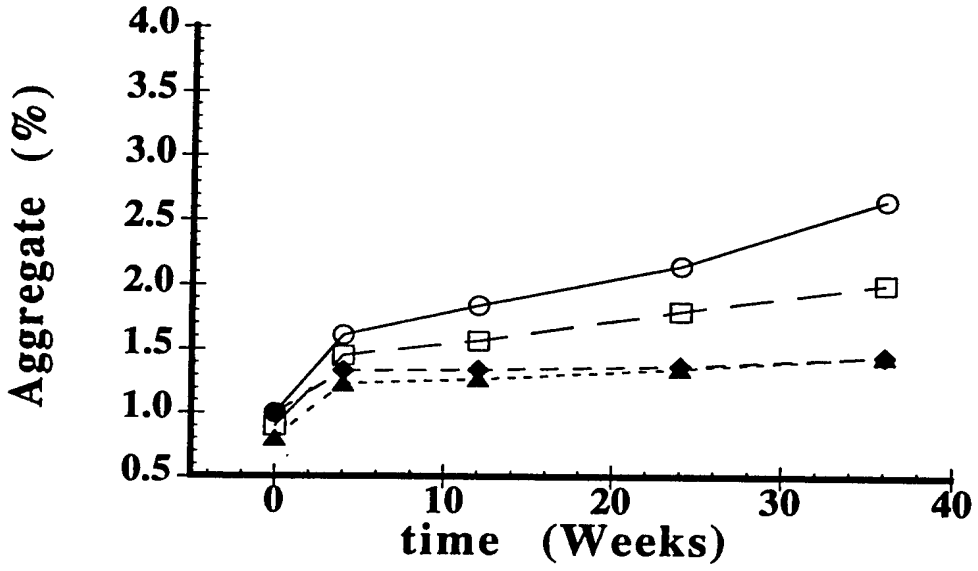


FIG. 18

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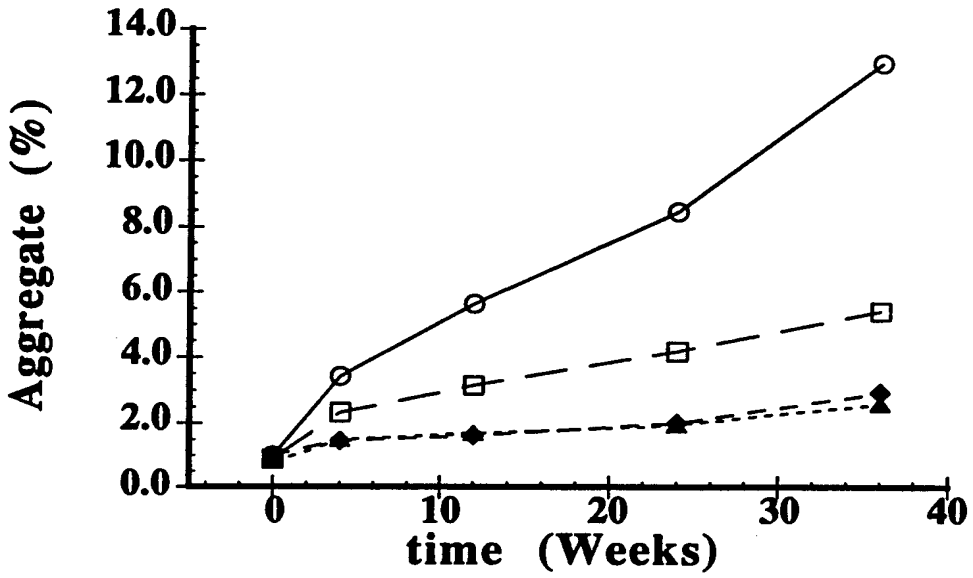


FIG. 19

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INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 96/12251

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K39/00 A61K39/395 C07K1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 661 060 A (IMMUNO AG) 5 July 1995 see the whole document ---	1,3,6, 8-12
A	WO 89 09402 A (TORAY INDUSTRIES INC.) 5 October 1989 see the whole document ---	1-3,6, 10,12
A	JOURNAL OF IMMUNOLOGICAL METHODS, vol. 181, no. 1, 12 April 1995, AMSTERDAM, NL, pages 37-43, XP002019425 P. DRABER ET AL.: "Stability of monoclonal IgM antibodies freeze-dried in the presence of trehalose." see abstract --- -/--	1-3,6, 10,12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 November 1996	03.12.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Nooij, F

Form PCT/ISA/210 (second sheet) (July 1992)

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF IMMUNOASSAY, vol. 16, no. 2, May 1995, NEW YORK, NY, USA, pages 183-197, XP000611616 K. NIELSEN ET AL.: "Stability of freeze-dried horseradish peroxidase-conjugated monoclonal antibodies used in diagnostic serology." see the whole document -----	1-3,6, 10,12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/12251

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-661060	05-07-95	DE-C-	4344824	31-08-95
		CA-A-	2138853	29-06-95
		CZ-A-	9403284	12-07-95
		FI-A-	946104	29-06-95
		HU-A-	70449	30-10-95
		JP-A-	7206709	08-08-95
		NO-A-	945045	29-06-95
WO-A-8909402	05-10-89	AT-T-	117434	15-02-95
		DE-D-	68920693	02-03-95
		DE-T-	68920693	24-05-95
		EP-A-	0365685	02-05-90
		US-A-	5262296	16-11-93

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Electronic Acknowledgement Receipt

EFS ID:	42070524
Application Number:	16739559
International Application Number:	
Confirmation Number:	1153
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-024CON10
Receipt Date:	02-MAR-2021
Filing Date:	10-JAN-2020
Time Stamp:	18:14:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	REGN-024CON10_2021-03-02_Supp_IDS_trans.pdf	50866 16dad05098d61fda422f508a3bc520145950a856	no	2

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-024CON10_2021-03-02_Supp_IDS.pdf	48661 e93eebb10d61b88f015e504045f78fcc98018af8	no	3
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Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	Petition_for_IPR_of_US_10464992_2021-01-07.pdf	1183585 b474931f8b150ce36180e4cbfb55fbb89da55c28	no	59
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4	Non Patent Literature	10464992_File_History.pdf	6226773 644dbf9989934865b94826981ea1491b50655bf1	no	124
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Information:					
5	Non Patent Literature	Gentz_Declaration.pdf	5149940 751d13e50171ef84c741467cd1759ef5b21c11c4	no	76
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6	Non Patent Literature	Fraser_2005.pdf	1131384 f84e936cfab3c957213b3459a7028198f26c1768	no	9
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7	Non Patent Literature	Wulff_2002.pdf	2232205 cfb6323385f7456a57d89ba67d898ebb30dc0495	no	11
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8	Non Patent Literature	COC_US_10464992.pdf	592885 21f0ce26da18c22cdee2d47d98e7db05d762835f	no	1
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Information:					

9	Non Patent Literature	Holash_2002.pdf	883870 1ffe9076b117653d70845276976b3beef987b857	no	6
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10	Non Patent Literature	USSN_12_835065_FH_Excerpt_Response.pdf	683681 ea993240d76bb2108d18a837034b59ed7cdc8868	no	4
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11	Non Patent Literature	USSN_12_835065_FH_Excerpt_Declaration.pdf	1516353 ecbd8c6eceedcfc7bc1960a9131b7ce38779c175	no	11
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12	Non Patent Literature	Gentz_CV.pdf	314553 ba731d7e5efb44094ece1386b1566b5028443fc3	no	3
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13	Non Patent Literature	Rudge_2005.pdf	179904 299e60e541e58d50a66a7177fddbb6958e7bdbbd	no	8
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14	Non Patent Literature	Chi_2003.pdf	729817 56856f1db245d6cd6dd3a5b4817eb9032c75f81a	no	12
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15	Non Patent Literature	Bontempo_1997.pdf	1755140 386b4e3b8155e7184a3fc1a5089c4bd022a371f7	no	20
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16	Non Patent Literature	Guidance_for_Industry_Q1A_R2.pdf	1578431 9b6dab384bba5a295f10172c297883cc9ec1e8b3	no	25
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17	Non Patent Literature	Parkins_and_Lashmar_2000.pdf	8867809 3226eb7ab80ec5371ecc814627124c69f756f220	no	9
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18	Non Patent Literature	Randolph_and_Jones_2002.pdf	1723828 aebc047c40eeb6a93b8210301425a9f9615fcbe9	no	17
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24	Non Patent Literature	Raptiva_Label.pdf	505838 315dd408f0257a5488e0652205716a01891840bb	no	36
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26	Non Patent Literature	Herceptin_Label.pdf	198314 401ac79d34ce4eef12daec3c2c516207b1b06354	no	2
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27	Non Patent Literature	Andersen_and_Krummen_2002.pdf	518774 3ea29e5082b40abb2ab6f7fd53fd71c8ad10e318	no	7
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28	Non Patent Literature	Janeway_2001.pdf	751780 aead3e5e6583d1127ff3c7f8b36b9d602df9f330	no	6
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29	Non Patent Literature	Drug_Vehicle_Code_C927.pdf	705638 168d2c7dcbc08b060292bf9c92cdc6a24c03f14a	no	1
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30	Non Patent Literature	Controls_in_SCI_experiments.pdf	765283 e944f8fc7593b359297af5b529074ad60b9b4512	no	2
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31	Foreign Reference	WO9704801_Genetech.pdf	2367942 d15eab6d53b35848015c750ee25079ae6e3025da	no	49
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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronically Filed 3/2/2021

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-024CON10
	Confirmation No.	1153
	First Named Inventor	Eric Furfine
	Application Number	16/739,559
	Filing Date	January 10, 2020
	Group Art Unit	
	Examiner Name	
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Title: "*VEGF Antagonist Formulations Suitable for Intravitreal Administration*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and a copies of the non-U.S.-patents and publications are also enclosed.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** Each item of information contained in the information disclosure statement was first cited in any communication from a foreign

patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☒ No fee is believed to be due.

☐ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-024CON10.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: March 2, 2021

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/739,559	01/10/2020	Eric FURFINE	REGN-024CON10

CONFIRMATION NO. 1153

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

POA ACCEPTANCE LETTER

OC000000123548655

Date Mailed: 02/24/2021

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 02/18/2021.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/qtran/

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 01/31/2018. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
16/739,559	January 10, 2020

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 96387

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Regeneron Pharmaceuticals, Inc.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	/Frank R. Cottingham/	Date (Optional)	
Name	Frank R. Cottingham		
Title	Executive Director, Assistant General Counsel, Patents, Regeneron Pharmaceuticals, Inc.		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Regeneron Pharmaceuticals, Inc.

Application No./Patent No.: 16/739,559 Filed/Issue Date: January 10, 2020

Titled: VEGF Antagonist Formulations Suitable for Intravitreal Administration

Regeneron Pharmaceuticals, Inc., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 053156, Frame 0704, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

   2. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Karl Bozicevic, Reg. No. 28,807/	2021-02-18
Signature	Date
Karl Bozicevic	28,807
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	41957561
Application Number:	16739559
International Application Number:	
Confirmation Number:	1153
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-024CON10
Receipt Date:	18-FEB-2021
Filing Date:	10-JAN-2020
Time Stamp:	14:31:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	5050US12_POA.pdf	163895 3f3756620d56bc069d67ad900cb3dc2cfeed01fd	no	1

Warnings:

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	REGN-024CON10-_2021-02-18_373c.pdf	118267 86389070a406a0462b33d3537fec4d6fa07021a9	no	3
Warnings:					
Information:					
		Total Files Size (in bytes):	282162		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/739,559	01/10/2020	Eric FURFINE	REGN-024CON10	1153

96387 7590 05/28/2020

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
LOCKARD, JON MCCLELLAND

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
05/28/2020	ELECTRONIC

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.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR/ PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
16/739,559	01/10/2020	FURFINE et al.	REGN-024CON10

		EXAMINER	
Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY, CA 94065		MARIANNE C SEIDEL	
		ART UNIT	PAPER
		1600	20200526

DATE MAILED: _____

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

Commissioner for Patents

The third-party submission under 37 CFR 1.290 filed on 5/22/2020 for the instant application has been determined to be compliant with 35 U.S.C. 122(e) and 37 CFR 1.290 and is being entered in the application. Please allow a few days for the submission to be visible in the Patent Application Information Retrieval (PAIR) system.

/MARIANNE C SEIDEL/
Quality Assurance Specialist, Art Unit 1600

PTO-90C (Rev.04-03)

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290
CONCISE DESCRIPTION OF RELEVANCE

Application Number	16739559

U.S. PATENTS

Cite No	Patent Number	Concise Description of Relevance
1	9340594	Concise Description uploaded as a separate document
2	7608261	Concise Description uploaded as a separate document
3	9580489	Concise Description uploaded as a separate document

U.S. PATENT APPLICATION PUBLICATION		
Cite No	**Publication Number**	**Concise Description of Relevance**

FOREIGN PATENT DOCUMENTS		
CiteNo	**Foreign Document Number**	**Concise Description of Relevance**
1	WO1998045331	Concise Description uploaded as a separate document

2	WO2000075319	Concise Description uploaded as a separate document

NON-PATENT PUBLICATIONS		
Cite No	**Reference**	**Concise Description of Relevance**
1	USPTO Communication on Ex Parte Reexamination of US10464992, pages 1-12, published 04/01/2020, USPTO, PUBLIC PAIR	Concise Description uploaded as a separate document

2	Ex Parte Request for Reexamination of US10464992, pages 1-70, published 02/11/2020, USPTO, PUBLIC PAIR	Concise Description uploaded as a separate document

PTO/SB/429(08-12)
Approved for use through 07/31/2015. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16739559

U.S. PATENTS				
Cite No	Patent Number	Kind Code[1]	Issue Date (YYYY-MM-DD)	First Named Inventor
1	9580489		2017-02-28	Eric FURFINE
2	7608261		2009-10-27	Eric Furfine
3	9340594		2016-05-17	Eric FURFINE

U.S. PATENT APPLICATION PUBLICATIONS				
Cite No	Publication Number	Kind Code[1]	Publication Date (YYYY-MM-DD)	First Named Inventor

FOREIGN PATENTS AND PUBLISHED FOREIGN PATENT APPLICATIONS						
Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[1]	Publication Date (YYYY-MM-DD)	Applicant, Patentee or First Named Inventor	T[5]
1	WO2000075319	WO		2000-12-14	Nicholas J. Papadopoulos	☐

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16739559

2	WO1998045331	WO		1998-10-15	Manuel Baca	☐

NON-PATENT PUBLICATIONS (e.g., journal article, Office action)

Cite No	Author (if any), title of the publication, page(s) being submitted, publication date, publisher (where available), place of publication (where available).	T[5]	E[6]
1	Ex Parte Request for Reexamination of US10464992, pages 1-70, published 02/11/2020, USPTO, PUBLIC PAIR	☐	☒
2	USPTO Communication on Ex Parte Reexamination of US10464992, pages 1-12, published 04/01/2020, USPTO, PUBLIC PAIR	☐	☒

STATEMENTS

The party making the submission is not an individual who has a duty to disclose information with respect to the above-identified application under 37 CFR 1.56.

This submission complies with the requirements of 35 U.S.C. 122(e) and 37 CFR 1.290.

THIRD-PARTY SUBMISSION UNDER 37 CFR 1.290	Application Number	16739559

☒ The fee set forth in 37 CFR 1.290(f) has been submitted herewith.

☐ The fee set forth in 37 CFR 1.290(f) is not required because this submission lists three or fewer total items and, to the knowledge of the person signing the statement after making reasonable inquiry, this submission is the first and the only submission under 35 U.S.C 122(e) filed in the above-identified application by the party making the submission or by a party in privity with the party.

☐ This resubmission is being made responsive to a notification of non-compliance issued for an earlier filed third-party submission. The corrections in this resubmission are limited to addressing the non-compliance. As such, the party making this resubmission: (1) requests that the Office apply the previously-paid fee set forth in 37 CFR 1.290(f), or (2) states that no fee is required to accompany this resubmission as the undersigned is again making the fee exemption statement set forth in 37 CFR 1.290(g).

Signature	/NGAM FUNG DAVID CHAN/		
Name/Print	NGAM FUNG DAVID CHAN	Registration Number (if applicable)	76820

Examiner Signature		Date Considered	

*EXAMINER: Signature indicates all documents listed above have been considered,except for citations through which a line is drawn. Draw line through citation if not considered. Include a copy of this form with next communication to applicant. 1. If known, enter kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16. See MPEP 901.04(a). 2. Enter the country or patent office that issued the document, by two-letter code under WIPO standard ST.3. See MPEP 1851. 3. For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 4. If known, enter the kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 . See MPEP 901.04(a). 5. Check mark indicates translation attached. 6. Check mark indicates evidence of publication attached.

Concise Description of Relevance of References Submitted by Third Party

The table on the following pages illustrate where and how the references submitted by the third party— US Patent No. 9,340,594 (hereinafter "P1"); US Patent No. 7,608,261 (hereinafter "P2"); US Patent No. 9,580,489 (hereinafter "P3"); International Patent Application Publication No. WO 00/75319 A1, published on Dec. 14, 2000 (herein after "P4"), and International Patent Application Publication No. WO 98/45331 A2, published on Oct. 15, 1998 (herein after "P5"); disclose the limitations of claims 1-9 of US Application No. 16/739,559, published as US2020/0131246 on Apr. 30, 2020, further evidenced by the request for re-examination (herein after "P6") of related US Patent No. 10,464,992 as received by USPTO on Feb. 11, 2020, and the communication from USPTO on Apr. 1, 2020 regarding institution of re-examination (herein after "P7"), where the re-examination is granted under control number US 90/014448.

Petitioner Fresenius Ex. 1004, 0221

Claims in Application US16/739,559, as published on April 30, 2020 (Priority 2006-06-16)	US9,340,594 (P1) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US7,608,261 (P2) (Priority: 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US9,580,489 (P3) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)
Claim 1 A pre-filled syringe comprising: a vascular endothelial growth factor (VEGF) antagonist, an organic co-solvent, a buffer, and a stabilizing agent, wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.	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, 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. Claim 3: The pre-filled syringe according to claim 2, wherein the VEGF trap is stable for at least 4 months. Claim 8: The pre-filled syringe according to claim 2 wherein the VEGF trap is stable for at least 5 months. WO 00/75319 A1 (P4) Modified chimeric polypeptides with improved pharmacokinetic properties (Title) Other included embodiments are a host-vector system for the production of a fusion polypeptide which comprises the expression vector, in a suitable host cell; … the host-vector system wherein the suitable host cell is a CHO cell. (Page 12 Lines 19-26)	Claim 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. Claim 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. Claim 8: A lyophilizable formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising a) 5-50 mg/ml of the VEGF antagonist, comprising the amino acid sequence of SEQ ID NO:4; b) 5-25 mM of sodium phosphate buffer, pH about 5.8-7.0; c) 0.01-0.15% of an organic co-solvent, selected from the group consisting of polysorbate, polyethylene glycol (PEG), propylene glycol, and a combination thereof; and, d) 1-10% of a stabilizing agent selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol. WO 00/75319 A1 (P4)	Claim 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. Claim 24: The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist is expressed in a Chinese hamster ovary (CHO) cell. WO 98/45331 A2 (P5) Anti-vegf antibodies (Title) Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The active agent in the composition is

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Claims in Application US16/739,559, as published on April 30, 2020 (Priority 2006-06-16)	US9,340,594 (P1) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US7,608,261 (P2) (Priority: 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US9,580,489 (P3) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)
	The first two cysteines in the Fc region (Cys211 and Cys214) form an intermolecular disulfide bond with the same two cysteines in another Fc chain. (Page 25 Lines 23-25) WO 98/45331 A2 (P5) Anti-vegf antibodies (Title) Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The active agent in the composition is the anti-VEGF antibody. (Page 47 lines 13-18)	Modified chimeric polypeptides with improved pharmacokinetic properties (Title) Other included embodiments are a host-vector system for the production of a fusion polypeptide which comprises the expression vector, in a suitable host cell; … the host-vector system wherein the suitable host cell is a CHO cell. (Page 12 Lines 19-26) The first two cysteines in the Fc region (Cys211 and Cys214) form an intermolecular disulfide bond with the same two cysteines in another Fc chain. (Page 25 Lines 23-25) WO 98/45331 A2 (P5) Anti-vegf antibodies (Title) Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The active agent in the composition is the anti-VEGF antibody. (Page 47 lines 13-18)	the anti-VEGF antibody. (Page 47 lines 13-18)
Claim 2 The pre-filled syringe of claim 1, wherein about 99% or more of the weight of the fusion protein is in native conformation.	*Same Analysis as Claim 1*	*Same Analysis as Claim 1*	*Same Analysis as Claim 1*

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Claims in Application US16/739,559, as published on April 30, 2020 (Priority 2006-06-16)	US9,340,594 (P1) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US7,608,261 (P2) (Priority: 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US9,580,489 (P3) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)
Claim 3 The pre-filled syringe 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.	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.	*Same Analysis as Claim 1*	Claim 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
Claim 4 The pre-filled syringe of claim 3, wherein the fusion protein comprises amino acids 27-457 of SEQ ID NO:4..	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.	Claim 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. Claim 8: A lyophilizable formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising	Claim 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.

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Claims in Application US16/739,559, as published on April 30, 2020 (Priority 2006-06-16)	US9,340,594 (P1) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US7,608,261 (P2) (Priority: 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US9,580,489 (P3) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)
		a) 5-50 mg/ml of the VEGF antagonist, comprising the amino acid sequence of SEQ ID NO:4; b) 5-25 mM of sodium phosphate buffer, pH about 5.8-7.0; c) 0.01-0.15% of an organic co-solvent, selected from the group consisting of polysorbate, polyethylene glycol (PEG), propylene glycol, and a combination thereof; and, d) 1-10% of a stabilizing agent selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.	
Claim 5 The pre-filled syringe of claim 4, wherein the VEGF antagonist is a dimer of the fusion protein.	*Same Analysis as Claim 1 and Claim 4*	*Same Analysis as Claim 1 and Claim 4*	23. The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist is a dimer.
Claim 6 The pre-filled syringe 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 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.	Claim 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. Claim 8: A lyophilizable formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising a) 5-50 mg/ml of the VEGF antagonist, comprising the amino acid sequence of SEQ ID NO:4;	Claim 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. 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%.

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Claims in Application US16/739,559, as published on April 30, 2020 (Priority 2006-06-16)	US9,340,594 (P1) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US7,608,261 (P2) (Priority: 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US9,580,489 (P3) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)
		b) 5-25 mM of sodium phosphate buffer, pH about 5.8-7.0; c) 0.01-0.15% of an organic co-solvent, selected from the group consisting of polysorbate, polyethylene glycol (PEG), propylene glycol, and a combination thereof; and, d) 1-10% of a stabilizing agent selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.	
Claim 7 The pre-filled syringe of claim 6, wherein the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.	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.	Claim 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. Claim 8: A lyophilizable formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising a) 5-50 mg/ml of the VEGF antagonist, comprising the amino acid sequence of SEQ ID NO:4; b) 5-25 mM of sodium phosphate buffer, pH about 5.8-7.0; c) 0.01-0.15% of an organic co-solvent, selected from the group consisting of polysorbate, polyethylene glycol (PEG), propylene glycol, and a combination thereof; and, d) 1-10% of a stabilizing agent selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.	Claim 19: The formulation of claim 1, comprising a stabilizer comprising trehalose or sucrose. Claim 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%.
Claim 8 The pre-filled syringe of claim 1, wherein the organic	Claim 5: The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF	Claim 1: An ophthalmic formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising	Claim 11: The formulation of claim 1, wherein the organic co-solvent comprises one or more of polysorbate 20, polysorbate 80,

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Claims in Application US16/739,559, as published on April 30, 2020 (Priority 2006-06-16)	US9,340,594 (P1) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US7,608,261 (P2) (Priority: 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US9,580,489 (P3) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)
co-solvent is polysorbate 20 and the stabilizing agent is sucrose.	trap, 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, at pH 6.2-6.4.	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. Claim 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. Claim 8: A lyophilizable formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising a) 5-50 mg/ml of the VEGF antagonist, comprising the amino acid sequence of SEQ ID NO:4; b) 5-25 mM of sodium phosphate buffer, pH about 5.8-7.0; c) 0.01-0.15% of an organic co-solvent, selected from the group consisting of polysorbate, polyethylene glycol (PEG), propylene glycol, and a combination thereof; and, d) 1-10% of a stabilizing agent selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol. Claim 9: The lyophilizable formulation of claim 8, comprising about 20 mg/ml of the VEGF antagonist, about 10 mM sodium phosphate buffer, about 0.03% polysorbate, about 0.1% PEG and	polyethylene glycol (PEG) 3350, and propylene glycol. 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%. Claim 19: The formulation of claim 1, comprising a stabilizer comprising trehalose or sucrose. Claim 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%.

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Claims in Application US16/739,559, as published on April 30, 2020 (Priority 2006-06-16)	US9,340,594 (P1) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US7,608,261 (P2) (Priority: 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US9,580,489 (P3) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)
		about 2.5% sucrose, pH about 6.2-6.3. Claim 10: The lyophilizable formulation of claim 8, comprising about 20 mg/ml of the VEGF antagonist, about 5 mM sodium phosphate buffer, about 0.015% polysorbate, about 2.5% sucrose, and further comprising sodium chloride at about 20 mM, pH about 6.2-6.3.	
Claim 9 The pre-filled syringe of claim 1, wherein the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose.	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.	Claim 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. Claim 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. Claim 8: A lyophilizable formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising a) 5-50 mg/ml of the VEGF antagonist, comprising the amino acid sequence of SEQ ID NO:4; b) 5-25 mM of sodium phosphate buffer, pH about 5.8-7.0;	Claim 6: The formulation of claim 1, wherein the buffer comprises a phosphate buffer. Claim 7: The formulation of claim 6, wherein the buffer comprises sodium phosphate present at a concentration of 10 mM. Claim 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. 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%. Claim 19: The formulation of claim 1, comprising a stabilizer comprising trehalose or sucrose. Claim 20: The formulation of claim 19, wherein the stabilizer comprises sucrose.

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Claims in Application US16/739,559, as published on April 30, 2020 (Priority 2006-06-16)	US9,340,594 (P1) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US7,608,261 (P2) (Priority: 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)	US9,580,489 (P3) (Priority 2006-06-16) VEGF antagonist formulations for intravitreal administration (Title)
		c) 0.01-0.15% of an organic co-solvent, selected from the group consisting of polysorbate, polyethylene glycol (PEG), propylene glycol, and a combination thereof; and, d) 1-10% of a stabilizing agent selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol. Claim 9: The lyophilizable formulation of claim 8, comprising about 20 mg/ml of the VEGF antagonist, about 10 mM sodium phosphate buffer, about 0.03% polysorbate, about 0.1% PEG and about 2.5% sucrose, pH about 6.2-6.3. Claim 10: The lyophilizable formulation of claim 8, comprising about 20 mg/ml of the VEGF antagonist, about 5 mM sodium phosphate buffer, about 0.015% polysorbate, about 2.5% sucrose, and further comprising sodium chloride at about 20 mM, pH about 6.2-6.3.	21. The formulation of claim 20, wherein the sucrose is present at a concentration of 5%.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re *Ex Parte* Reexamination of:	Furfine et al.
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U.S. Patent No.:	10,464,992
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Title:	VEGF Antagonist Formulations Suitable for Intravitreal Administration

VIA EFS
Mail Stop "Ex Parte Reexam"
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
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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35 U.S.C. § 154 1

35 U.S.C. § 301 1

35 U.S.C. § 302 18

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EXHIBIT LIST

Exhibit No.	*Document Description*
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)

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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.

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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 immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and
>
> wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5ºC. 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.

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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 5ºC. 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

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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 5ºC 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 5ºC:

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.

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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-FcΔC1(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 "hFCΔC1A" 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.FcΔC1(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-FcΔC1(a) [*i.e.,* the protein of SEQ ID NO: 4 of the '992 Patent]." *Id.* at 82:12-13.

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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 5ºC 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.

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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

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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 5ºC 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 5ºC 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.

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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-FcΔC1(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).

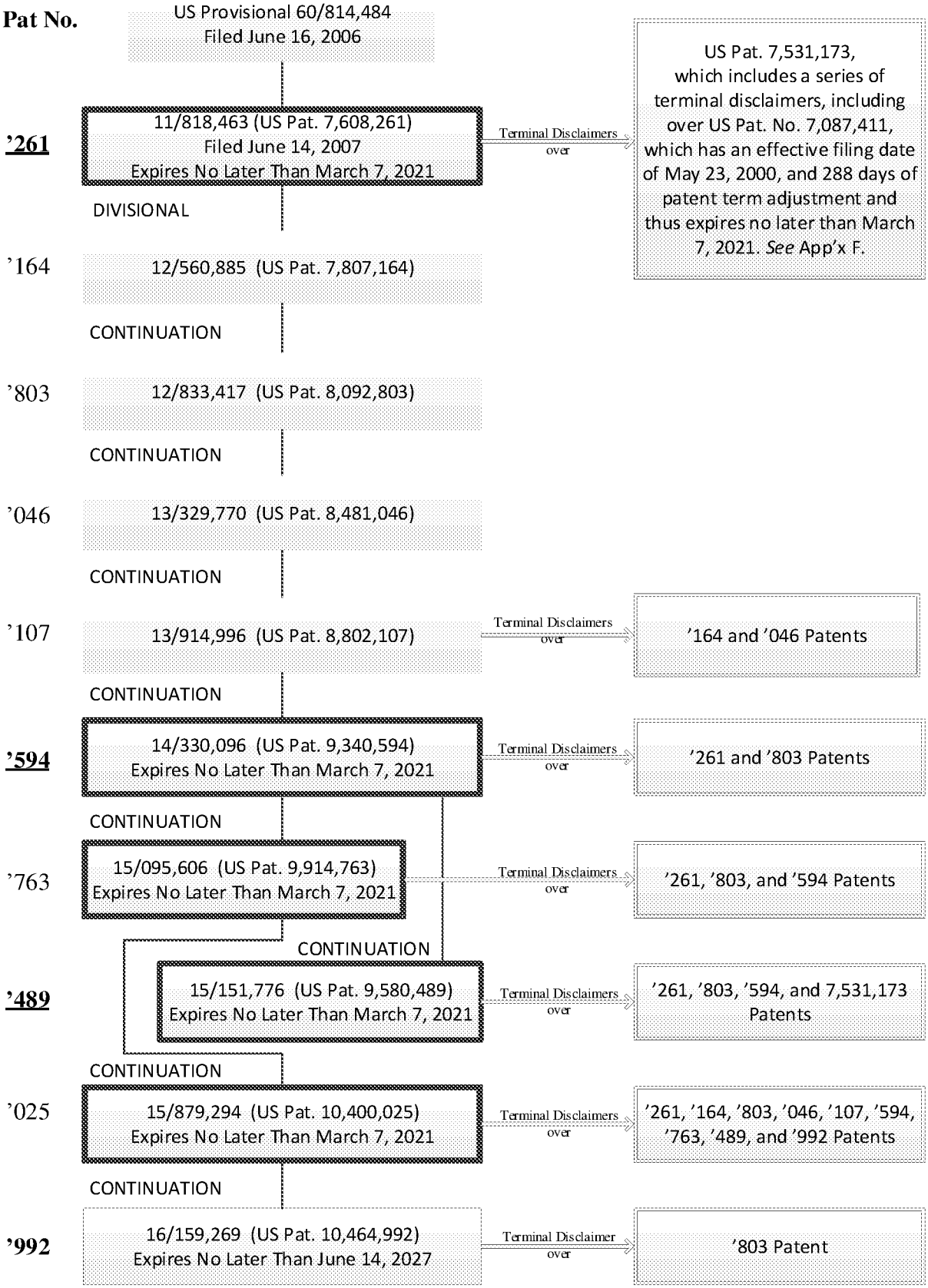
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9. **PCT Publication No. WO 00/63380 A1 to Cunningham et al. (Exhibit 10)** published October 26, 2000 from PCT App. No. PCT/US00/09483. Cunningham et al. is prior art to the '992 Patent under 35 U.S.C. § 102(b).

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:

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Pat No.
US Provisional 60/814,484
Filed June 16, 2006
'261
11/818,463 (US Pat. 7,608,261)
Filed June 14, 2007
Expires No Later Than March 7, 2021
Terminal Disclaimers over
US Pat. 7,531,173, which includes a series of terminal disclaimers, including over US Pat. No. 7,087,411, which has an effective filing date of May 23, 2000, and 288 days of patent term adjustment and thus expires no later than March 7, 2021. See App'x F.
DIVISIONAL
'164
12/560,885 (US Pat. 7,807,164)
CONTINUATION
'803
12/833,417 (US Pat. 8,092,803)
CONTINUATION
'046
13/329,770 (US Pat. 8,481,046)
CONTINUATION
'107
13/914,996 (US Pat. 8,802,107)
Terminal Disclaimers over
'164 and '046 Patents
CONTINUATION
'594
14/330,096 (US Pat. 9,340,594)
Expires No Later Than March 7, 2021
Terminal Disclaimers over
'261 and '803 Patents
CONTINUATION
'763
15/095,606 (US Pat. 9,914,763)
Expires No Later Than March 7, 2021
Terminal Disclaimers over
'261, '803, and '594 Patents
CONTINUATION
'489
15/151,776 (US Pat. 9,580,489)
Expires No Later Than March 7, 2021
Terminal Disclaimers over
'261, '803, '594, and 7,531,173 Patents
CONTINUATION
'025
15/879,294 (US Pat. 10,400,025)
Expires No Later Than March 7, 2021
Terminal Disclaimers over
'261, '164, '803, '046, '107, '594, '763, '489, and '992 Patents
CONTINUATION
'992
16/159,269 (US Pat. 10,464,992)
Expires No Later Than June 14, 2027
Terminal Disclaimer over
'803 Patent

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

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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

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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

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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*.

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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.

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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

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[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

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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-

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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.

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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.

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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 immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and
>
> wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5ºC 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

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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 5ºC 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. *See, e.g.*, 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 (CHO) cell, the fusion protein comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and	'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 5ºC 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.

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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

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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 5ºC 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

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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 5ºC 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

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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

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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

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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

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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 Fltl and the second VEGF receptor is selected from the group consisting of human Flkl 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 Fltl and the second VEGF receptor is selected from the group consisting of human Flkl 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.

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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

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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**,

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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.

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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 5ºC 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. *See, e.g.*, Exemplary Vial Pubs (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"

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wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and	'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 5ºC 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 5ºC 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 immunoglobin-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.

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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 5ºC 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**

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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 5ºC 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).

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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.

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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:

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> 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).

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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.

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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

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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

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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"

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wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and	'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 5ºC 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. *See* Table *infra*.

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

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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)

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pH 6.3	"the pH is about **pH 6.2-6.3**" (claim 9)

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

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conformation following storage at 5ºC 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]

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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

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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):

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REGENERON - BOZICEVIC, FIELD & FRANCIS LLP

201 Redwood Shores Parkway, Suite 200

Redwood City, CA 94065

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
Attorney for Requester
Registration No. 53,255
MAIER & MAIER, PLLC

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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. *See, e.g.*, 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

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(CHO) cell, the fusion protein comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and	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 5ºC 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. *See, e.g.*,'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).

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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 Fltl and the second VEGF receptor is selected from the group consisting of human Flkl 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. *See, e.g.*, 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 immunoglobin-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 5ºC 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. *See, e.g.* '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; *see also* '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 Fltl and the second VEGF receptor is selected from the group consisting of human Flkl 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 immunoglobin-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

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in native conformation following storage at 5ºC 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**."

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 Fltl and the second VEGF receptor is selected from the group consisting of human Flkl 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**"

Petitioner Fresenius Ex. 1004, 0303

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**"

Petitioner Fresenius Ex. 1004, 0304

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%

SEQ4of992       1 MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTS
SEQ11           1 MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTS
                  ************************************************************

SEQ4of992      61 PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLT
SEQ11          61 PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLT
                  ************************************************************

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 TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
SEQ11         361 TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
                  ************************************************************

SEQ4of992     421 LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ11         421 LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
                  ***************************************
```

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  MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTS
SeqID4-992     1  MVSYWDTGVLLCALLSCLLLTGSSSGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTS

WO319_FIG_24  61 PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLT
SeqID4-992    61 PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLT

WO319_FIG_24 121 HRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRD
SeqID4-992   121 HRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRD

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

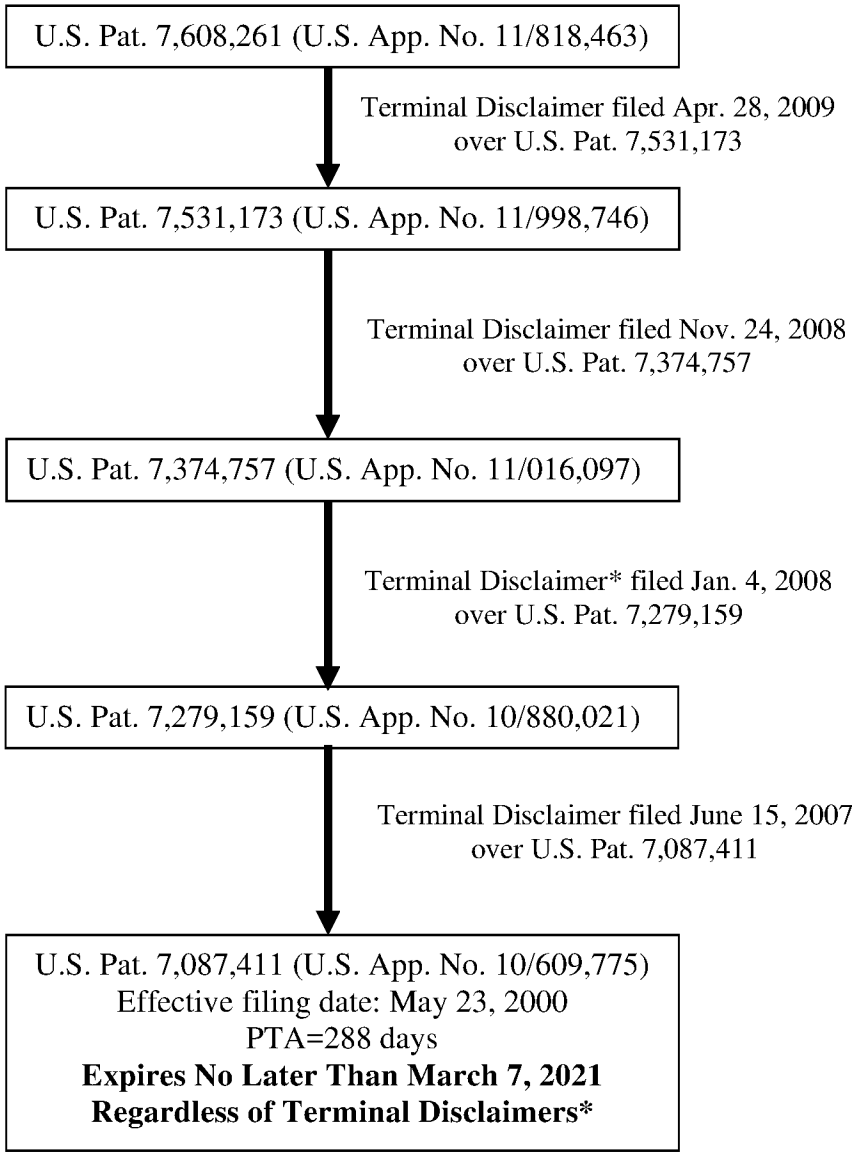
WO319_FIG_24 361 TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
SeqID4-992   361 TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK

WO319_FIG_24 421 LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SeqID4-992   421 LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
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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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/014,448	02/11/2020	10464992	13850001REEX	5306

96387 7590 04/01/2020

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER
TURNER, SHARON L

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
04/01/2020	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.	Patent Under Reexamination	
	90/014,448	10464992	
	Examiner	Art Unit	AIA (FITF) Status
	SHARON L TURNER	3991	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.

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 immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5.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 immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5.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 Al, 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 Al, 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 NaCI, 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-FcΔC1(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.Flk1D3.FcΔC1(a) and VEGFR1R2- FcΔC1(a) (26:12-25). CHO cell culture production, harvest and purification of Flt1D2.Flk1D3.FcΔC1(a) is taught in Example 21-22, particularly (67:25-68:5, 70:23-24). CHO transiently expressed Flt1 D2.Flk1D3.FcΔC1(a), CHO stably expressed Flt1D2.Flk1D3.FcΔC1 (a), and CHO transiently expressed VEGFR1R2-FcΔC1(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 Papadopolous, 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
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By FAX to: (571) 273-9900
Central Reexamination Unit

By hand to: Customer Service Window
Randolph Building
401 Dulany St.
Alexandria, VA 22314

/Sharon Turner/
Patent Reexamination Specialist
Central Reexamination Unit 3991

Conferees:

/Bruce Campell/
Patent Reexamination Specialist
Central Reexamination Unit 3991

/TIMOTHY M SPEER/
Supervisory Patent Examiner, Art Unit 3991

Reexamination	Application/Control No.	Applicant(s)/Patent Under Reexamination
	90/014,448	10464992
	Certificate Date	Certificate Number

Requester Correspondence Address: ☐	Patent Owner ☑	Third Party

MAIER & MAIER, PLLC
345 SOUTH PATRICK STREET
ALEXANDRIA, VA 22314

LITIGATION REVIEW ☑	ST (examiner initials)	03 March 2020 (date)
Case Name		Director Initials
None		

COPENDING OFFICE PROCEEDINGS	
TYPE OF PROCEEDING	NUMBER
None	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	90/014,448	10464992
	Examiner	Art Unit
	SHARON L TURNER	3991

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Litigation Search - None	03/08/2020	ST
Prosecution History 16/159,269	03/11/2020	ST

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16159269
Filing Date	2018-10-12
First Named Inventor	Eric FURFINE
Art Unit	
Examiner Name	
Attorney Docket Number	13850001REEX

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.L.T/

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	7,608,261	B2	2009-10-27	Furfine et al.	Throughout
	2	9,340,594	B2	2016-05-17	Regeneron Pharmaceuticals, Inc.	Throughout
	3	9,914,763	B2	2018-03-13	Regeneron Pharmaceuticals, Inc.	Throughout
	4	10,400,025	B2	2019-09-03	Regeneron Pharmaceuticals, Inc.	Throughout
	5	9,580,489	B2	2017-02-28	Regeneron Pharmaceuticals, Inc.	Throughout
	6	10,464,992	B2	2019-11-05	Regeneron Pharmaceuticals, Inc.	Throughout

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16159269
	Filing Date	2018-10-12
	First Named Inventor	Eric FURFINE
	Art Unit	
	Examiner Name	
	Attorney Docket Number	13850001REEX

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.L.T/

	1	20160144025	A1	2016-05-26	Regeneron Pharmaceuticals, Inc.	paragraphs [0086], [0197]

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	00/75319	WO	A1	2000-12-14	Regeneron Pharmaceuticals, Inc.	Throughout	
	2	98/45331	WO	A2	1998-10-15	GENENTECH, INC.	Throughout	
	3	00/63380	WO	A1	2000-10-26	GENENTECH, INC.	Throughout	

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	~~Prosecution history for U.S. Patent No. 10,464,992 (U.S. Patent Application No. 16/159,269)~~	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/SHARON L TURNER/	Date Considered	03/08/2020

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16159269
	Filing Date	2018-10-12
	First Named Inventor	Eric FURFINE
	Art Unit	
	Examiner Name	
	Attorney Docket Number	13850001REEX

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16159269
Filing Date	2018-10-12
First Named Inventor	Eric FURFINE
Art Unit	
Examiner Name	
Attorney Docket Number	13850001REEX

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Christopher J. Maier/	Date (YYYY-MM-DD)	2020-02-11
Name/Print	Christopher J. Maier	Registration Number	53,255

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	16739559
Filing Date:	
Title of Invention:	
First Named Inventor/Applicant Name:	
Filer:	Ngam Fung David Chan
Attorney Docket Number:	

Filed as Large Entity

Filing Fees for

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
DOCUMENT FEE FOR THIRD-PARTY SUBMISSIONS	1818	1	180	180
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**180**

Electronic Acknowledgement Receipt

EFS ID:	39523754
Application Number:	16739559
International Application Number:	
Confirmation Number:	1153
Title of Invention:	
First Named Inventor/Applicant Name:	
Correspondence Address:	- - - - - - - - - -
Filer:	Ngam Fung David Chan
Filer Authorized By:	
Attorney Docket Number:	
Receipt Date:	22-MAY-2020
Filing Date:	
Time Stamp:	19:36:00
Application Type:	

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$180

RAM confirmation Number	E20205LJ35598974
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Concise Description of Relevance	Concise-description-generated.pdf	35135 96ba90ce33bfe77e449082d1c0413a73d052688b	no	4
Warnings:					
Information:					
2	Third-Party Submission Under 37 CFR 1.290	Third-party-preissuance-submission.pdf	49294 bc0b4206ba5b5e1f23285d244a8a9dcf7153ce62	no	3
Warnings:					
Information:					
3	Request for Notification of Non-compliant Third-Party Submission	Third-party-notification-request.pdf	19570 b8af5885f7635cbff7988b87dd91ff74c893609f	no	1
Warnings:					
Information:					
4	Concise Description of Relevance	Third_Party_Submission_against_US16_739559.pdf	142998 593acc24eb8327ee4fb4291ab33d402d641b276c	no	9
Warnings:					
Information:					
5	Evidence of Publication	90014448_Request_for_Reexamination_of_US10464992.pdf	3648837 59743e6cc699e0ce373f602d0ada159ea86d42ff	no	78
Warnings:					
Information:					

6	Evidence of Publication	90014448_Communication_of_Reexamination_of_US10464992.pdf	801642 6f1b2051d98753e31509e429acee0ad8140e3552	no	21
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	29486 932259564d46f0d0a71e1ea99c16b67df0bc6c70	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	4726962		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/739,559	01/10/2020	Eric FURFINE	REGN-024CON10

CONFIRMATION NO. 1153

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

PUBLICATION NOTICE

OC000000116636802

Title:VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

Publication No.US-2020-0131246-A1
Publication Date:04/30/2020

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/739,559
				Filing Date	2020-01-10
				First Named Inventor	Eric Furfine
				Art Unit	
				Examiner Name	
Sheet	1	of	2	Attorney Docket Number	REGN-024CON10

U.S. PATENT DOCUMENTS					
Examiner Initial*	Cite No.	Patent Number Number-Kind Code (*if known*)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	**6100071**	2000-08-08	Davis-Smyth et al.	
	2	**6897294**	2005-05-24	Davis-Smyth et al.	
	3	**7052691**	2006-05-30	Sleeman et al.	

U.S. PATENT APPLICATION PUBLICATIONS					
Examiner Initial*	Cite No.	Publication Number **Number-Kind Code** (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	**20050281831**	2005-12-22	Davis-Smyth et al.	
	2	**20060217311**	2006-09-28	Dix et al.	
	3	**20080085276**	2008-04-10	Wiegand et al.	
	4	**20140012227**	2014-01-09	Sigg et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (*if known*)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1	WO 97/04801	1997-02-13	Genentech, Inc.		
	2	JPH11510170	1999-09-07	Genentech, Inc.	See WO 97/04801 for English Equivalent	X
	3	WO 99/62536	1999-12-09	Celtrix Pharmaceuticals, Inc.		
	4	JP 10273450	1998-10-13	Toagosei Co. Ltd.	See WO 99/62536 for English Equivalent	X
	5	WO 99/62536	1999-12-09	Celtrix Pharmaceuticals, Inc.		
	6	JP2002516871	2002-06-11	Celtrix Pharmaceuticals, Inc.	See WO 99/62536 for English Equivalent	X
	7	WO 2004/091658	2004-10-28	Genentech, Inc.		
	8	WO 2005/000895	2005-01-06	Regeneron Pharmaceuticals, Inc.		
	9	WO 2005011734	2005-02-10	Regeneron Pharmaceuticals, Inc.		
	10	WO 2005/020972	2005-03-10	Eyetech Pharmaceuticals, Inc.		
	11	WO 2006/047325	2006-05-04	Genentech, Inc.		
	12	WO 2006/088650	2006-08-24	Regeneron Pharmaceuticals, Inc.		
	13	WO 2006/104852	2006-10-05	Regeneron Pharmaceuticals, Inc.		

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	16/739,559
				Filing Date	2020-01-10
				First Named Inventor	Eric Furfine
				Art Unit	
				Examiner Name	
Sheet	2	of	2	Attorney Docket Number	REGN-024CON10

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	FRASER, Hamis M., et al., "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produced Prolonged, Dose-Related Suppression of Ovarian Function," (2004) J. Clin. Endocrin. & Metabol. 90(2):1114-1122	
	2	ANONYMOUS: "Lucentis in the treatment of neovascular (wet) age-related macular degeneration (AMD)", 1 January 2007, pages 1-54	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Electronic Acknowledgement Receipt

EFS ID:	39121517
Application Number:	16739559
International Application Number:	
Confirmation Number:	1153
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-024CON10
Receipt Date:	10-APR-2020
Filing Date:	10-JAN-2020
Time Stamp:	11:05:25
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	REGN-024CON10_2020-04-10_IDS_trans.pdf	52086 327c74f177722f10a5942da2a1876bf06ee73b57	no	2

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-024CON10_2020-04-10_IDS.pdf	32158 70966382c42b8647cf81df1efe41af364dfcd96e	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
			Total Files Size (in bytes):	84244	

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New Applications Under 35 U.S.C. 111

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronically Filed 04/10/2020

INFORMATION DISCLOSURE STATEMENT	Attorney Docket No.	REGN-024CON10
	Confirmation No.	1153
	First Named Inventor	Eric Furfine
	Application Number	16/739,559
	Filing Date	January 10, 2020
	Group Art Unit	
	Examiner Name	
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Title: "*VEGF Antagonist Formulations Suitable for Intravitreal Administration*"	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A and a copies of a foreign patent is also enclosed.

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

All of the references identified herein were disclosed in parent application serial number 16/582,486, and as such, copies thereof are not included pursuant to the provisions of 37 CFR § 1.98(d).

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

☐ **IDS Statement under 37 CFR § 1.97(e)(1):** Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement; or

☐ **IDS Statement under 37 CFR § 1.97(e)(2):** No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

Fees

☒ No fee is believed to be due.

☐ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-024CON10.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: April 10, 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/739,559

APPLICATION AS FILED - PART I

	(Column 1)	(Column 2)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE($)	FEE($)		RATE($)	FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	9 minus 20 =	*			OR	x 100 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 460 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1720

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/739,559	01/10/2020		1720	REGN-024CON10	9	1

CONFIRMATION NO. 1153

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

FILING RECEIPT

OC000000114126185

Date Mailed: 01/23/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Eric FURFINE, Concord, MA;
Daniel DIX, LaGrangeville, NY;
Kenneth GRAHAM, Pleasant Valley, NY;
Kelly FRYE, Mendham, NJ;

Applicant(s)

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY;

Assignment For Published Patent Application

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 16/582,486 09/25/2019
which is a CON of 16/159,269 10/12/2018 PAT 10464992
which is a CON of 15/879,294 01/24/2018 PAT 10400025
which is a CON of 15/095,606 04/11/2016 PAT 9914763
which is a CON of 14/330,096 07/14/2014 PAT 9340594
which is a CON of 13/914,996 06/11/2013 PAT 8802107
which is a CON of 13/329,770 12/19/2011 PAT 8481046
which is a CON of 12/833,417 07/09/2010 PAT 8092803
which is a CON of 12/560,885 09/16/2009 PAT 7807164
which is a DIV of 11/818,463 06/14/2007 PAT 7608261
which claims benefit of 60/814,484 06/16/2006

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 01/22/2020
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/739,559**
Projected Publication Date: 04/30/2020
Non-Publication Request: No
Early Publication Request: No
Title

VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign

patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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Petitioner Fresenius Ex. 1004, 0345

RAW SEQUENCE LISTING

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Petitioner Fresenius Ex. 1004, 0347

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Petitioner Fresenius Ex. 1004, 0350

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Petitioner Fresenius Ex. 1004, 0351

Electronically Filed 1/10/2020

PRELIMINARY AMENDMENT Under 37 CFR § 1.115	Attorney Docket No.	REGN-024CON10
	Confirmation No.	
	First Named Inventor	Eric Furfine
	Application Number	
	Filing Date	January 10, 2020
Address to: Mail Stop Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Group Art Unit	
	Examiner Name	
	Title: "*VEGF Antagonist Formulations Suitable for Intravitreal Administration*"	

Sir:

Prior to the examination of the above-referenced application on the merits, please enter the amendments below.

ABSTRACT

[0066] Ophthalmic formulations of a vascular endothelial growth factor (VEGF)-specific fusion protein antagonist are provided suitable for intravitreal administration to the eye. The ophthalmic formulations include a stable liquid formulation and a lyophilizable formulation. Preferably, the protein antagonist has an amino acid sequence of SEQ ID NO:4.

WE CLAIM:

1. A prefilled glass syringe suitable for intravitreal administration containing a stable ophthalmic 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 protein produced in a Chinese Hamster Ovary (CHO) cell.

2. The prefilled glass syringe of claim 1, wherein 90% or more of the weight of the protein is not present as an aggregate.

3. The prefilled glass syringe of claim 2, wherein the protein is a fusion protein comprising the immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.

4. The prefilled glass syringe of claim 3, wherein the first VEGF receptor is the human Flt1 and the second VEGF receptor is the human Flk1 or the human Flt4.

5. The prefilled glass syringe of claim 4, wherein the fusion protein comprises an amino acid sequence of SEQ ID NO:4.

6. The prefilled glass syringe of claim 5, wherein the VEGF antagonist is a dimer of the fusion protein.

7. The prefilled syringe of claim 1, wherein the organic co-solvent is selected from the group consisting of polysorbate 20, polysorbate 80, polyethylene glycol (PEG), PEG3350, and propylene glycol.

8. The prefilled syringe of claim 1, wherein the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.

9. The prefilled syringe of claim 1, wherein the buffer comprises phosphate.

10. The prefilled syringe of claim 4 comprising (a) 1-100 mg/ml of the VEGF antagonist; (b) 0.01-5% of the organic co-solvent; (c) 5-40 mM of the buffer; and (d) 1.0-10% of the stabilizing agent.

11. The prefilled syringe of claim 11, wherein the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose.

VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

Cross-Reference to Related Applications

[0001] This application is a continuation application of U.S. patent application Ser. No. 14/330,096, filed July 14, 2014, which is a continuation of U.S. patent application Ser. No. 13/914,996, filed Jun. 11, 2013, which issued as U.S. Pat. No. 8,802,107 on Aug. 12, 2014, which is a continuation application of U.S. patent application Ser. No. 13/329,770, filed Dec. 19, 2011, which issued as U.S. Pat. No. 8,481,046 on Jul. 9, 2013, which is a continuation application of U.S. patent application Ser. No. 12/833,417, filed Jul. 9, 2010, which issued as U.S. Pat. No. 8,092,803 on Jan. 10, 2012, which is a continuation application of U.S. patent application Ser. No. 12/560,885, filed Sep. 16, 2009, which issued as U.S. Pat. No. 7,807,164 on Oct. 5, 2010, which is a divisional application of U.S. patent application Ser. No. 11/818,463, filed Jun. 14, 2007, which issued as U.S. Pat. No. 7,608,261 on Oct. 27, 2009, which claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 60/814,484, filed 16 Jun. 2006, which applications are each hereby incorporated by reference.

BACKGROUND OF INVENTION

Field of the Invention

[0002] The present invention is directed to pharmaceutical formulations suitable for intravitreal administration comprising agents capable of inhibiting vascular endothelial growth factor (VEGF), and to methods for making and using such formulations. The invention includes liquid pharmaceutical formulations having increased stability, as well as formulations that may be lyophilize and reconstituted for intravitreal administration.

Statement of Related Art

[0003] Vascular endothelial growth factor (VEGF) expression is nearly ubiquitous in human cancer, consistent with its role as a key mediator of tumor neoangiogenesis. Blockade of VEGF function, by binding to the molecule or its VEGFR-2 receptor, inhibits growth of implanted tumor cells in multiple different xenograft models (see, for example, Gerber et al. (2000) Cancer Res. 60:6253-6258). A soluble VEGF-specific fusion protein antagonist, termed a "VEGF trap" has been described (Kim et al. (2002) Proc. Natl. Acad. Sci. USA 99:11399-404; Holash et al. (2002) Proc.

Natl. Acad. Sci. USA 99:11393-8), which applications are specifically incorporated by reference in their entirety.

[0004] Ophthalmic formulations are known, see for example, U.S. 7,033,604 and 6,777,429. An ophthalmic formulation of a VEGF antibody is described in US 6,676,941.

[0005] Lyophilization (freeze drying under controlled conditions) is commonly used for long-term storage of proteins. The lyophilized protein is substantially resistant to degradation, aggregation, oxidation, and other degenerative processes while in the freeze-dried state (see, for example, U.S. 6,436,897).

BRIEF SUMMARY OF THE INVENTION

[0006] Stable formulations of a VEGF-specific fusion protein antagonist are provided. Pharmaceutically acceptable formulations are provided that comprise a VEGF "trap" antagonist with a pharmaceutically acceptable carrier. In specific embodiments, liquid and lyophilized formulations are provided.

[0007] In a first aspect, a stable liquid ophthalmic formulation of a VEGF-specific fusion protein antagonist is provided, comprising a fusion protein that comprises a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component (also termed a "VEGF trap"). In a specific embodiment of the VEGF-specific fusion protein antagonist, the first VEGF receptor is Flt1 and the second VEGF receptor is Flk1 or Flt4. In a more specific embodiment the fusion protein has the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4. Preferably, the VEGF antagonist is a dimer comprising two fusion proteins of SEQ ID NO:4.

[0008] In one aspect, a stable liquid ophthalmic formulation is provided that comprises 1-100 mg/ml VEGF-specific fusion protein antagonist, 0.01-5% of one or more organic co-solvent(s), 30-150 mM of one or more tonicity agent(s), 5-40 mM of a buffering agent, and optionally, 1.0-7.5% of a stabilizing agent, pH between about 5.8-7.0.

[0009] In one or more specific embodiments, 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; the tonicity agent may be, for example, sodium chloride or potassium chloride; the stabilizing agent may be sucrose, sorbitol, glycerol, trehalose, or mannitol; and the buffering agent may be, for example, phosphate buffer. In a specific embodiment,

the phosphate buffer is a sodium phosphate buffer.

[0010] In various embodiments, the organic co-solvent is polysorbate and/or PEG, the stabilizing agent is sucrose, the buffering agent is phosphate buffer, and the tonicity agent is sodium chloride.

[0011] More specifically, the stable liquid ophthalmic formulation comprises about 40-50 mg/ml of the VEGF antagonist (SEQ ID NO:4), about 10 mM phosphate buffer, 0.01-3% polysorbate and/or PEG, 40-135 mM sodium chloride, and optionally 5.0% sucrose, pH about 6.2-6.3.

[0012] In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 50 mg/ml of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 50 mM sodium chloride, 0.1% polysorbate, and 5% sucrose, pH about 6.2-6.3.

[0013] In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 50 mg/ml of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 50 mM sodium chloride, 3% PEG, and 5% sucrose, pH about 6.2-6.3.

[0014] In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 40 mg/ml of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 40 mM sodium chloride, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3.

[0015] In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 40 mg/ml of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 135 mM sodium chloride, and 0.03% polysorbate, pH about 6.2-6.3.

[0016] In another aspect, a stable liquid ophthalmic formulation is provided that comprises 1-100 mg/ml VEGF-specific fusion protein antagonist; 0.01-5% of one or more organic co-solvent(s); 5-40 mM of a buffering agent; and optionally 30-150 mM of one or more tonicity agent(s) and/or 1.0-7.5% of a stabilizing agent; having a pH between about 5.8-7.0.

[0017] In various embodiments, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 10 to about 80 mg/ml. In various embodiments, the VEGF antagonist (SEQ ID NO:4) 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. In a preferred embodiment, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 40 mg/ml.

[0018] In another embodiment, the stabilizing agent is selected from one or more of sucrose, sorbitol, glycerol, trehalose, and mannitol.

[0019] In another embodiment, the organic co-solvent is selected from one or more of polysorbate, for example, polysorbate 20 or polysorbate 80, polyethylene glycol (PEG), for example, PEG 3350, and propylene glycol.

[0020] In another embodiment, the buffer is a phosphate buffer, for example, sodium phosphate.

[0021] In another embodiment, the tonicity agent is a salt, for example, sodium chloride.

[0022] In one embodiment, the stable liquid ophthalmic formulation comprises 10 mM sodium phosphate buffer, about 0.03 to about 0.1% polysorbate and/or about 3% PEG or propylene glycol, about 40 mM sodium chloride, and about 5% sucrose. In a specific embodiment, the stable liquid ophthalmic formulation comprises 10 mM sodium phosphate buffer, about 0.03% polysorbate, about 40 mM sodium chloride, and about 5% sucrose. In another specific embodiment, the pH of the formulation is about 6.2 to about 6.3. In another specific embodiment, the pH is achieved by mixing mono- and dibasic sodium phosphate to the desired pH without acid/base titration.

[0023] In a specific embodiment, the stable liquid ophthalmic formulation consists essentially of a VEGF antagonist (SEQ ID NO:4) at 40 mg/ml, 10 mM sodium phosphate buffer, polysorbate at 0.03%, sodium chloride at 40 mM, and sucrose at 5%, pH 6.2-6.3.

[0024] In another aspect, a stable liquid ophthalmic formulation is provided that comprises about 10 to about 80 mg/ml VEGF antagonist, about 10 mM sodium phosphate buffer, about 0.03% polysorbate, and about 135 mM sodium chloride, pH 6.2 to 6.3.

[0025] In various embodiments, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 10 to about 80 mg/ml. In various embodiments, the VEGF antagonist (SEQ ID NO:4) 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. In a specific embodiment, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 40 mg/ml.

[0026] In one embodiment, the stable liquid ophthalmic formulation comprises 40 mg/ml of VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 0.03% polysorbate, and 135 mM sodium chloride at pH 6.2-6.3. In a specific embodiment, the stable liquid ophthalmic formulation consists essentially of 40 mg/ml of VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 0.03% polysorbate, and 135 mM sodium chloride at pH 6.2-6.3.

[0027] In another aspect, a lyophilizable formulation of a VEGF antagonist is provided, wherein upon lyophilization followed by reconstitution, a stable liquid ophthalmic formulation as described

herein is obtained.

[0028] In another aspect, a lyophilizable formulation of a vascular endothelial growth factor (VEGF)-specific fusion protein antagonist is provided, comprising 5-50 mg/ml of the VEGF antagonist, 5-25 mM buffer, such as phosphate buffer, 0.01 to 0.15% of one or more of an organic co-solvent, such as polysorbate, propylene glycol and/or PEG, and optionally 1-10% of a stabilizing agent such as sucrose, sorbitol, trehalose, glycerol, or mannitol, pH about 5.8-7.0. In various embodiments, the VEGF antagonist (SEQ ID NO:4) is present at about 5, about 10, about 20, about 30, or about 40 mg/ml. In a specific embodiment, the lyophilizable ophthalmic formulation of the invention comprises 20 mg/ml of the VEGF antagonist, 10 mM sodium phosphate buffer, 0.03% polysorbate, 0.1% PEG, and 2.5% sucrose, pH about 6.2-6.3. In further embodiments, the lyophilizable formulation further comprises sodium chloride. In a specific embodiment, the sodium chloride is present at a concentration of about 20 mM. In another specific embodiment, the sodium chloride is present at a concentration of about 67.5 mM.

[0029] In another specific embodiment, the lyophilizable ophthalmic formulation of the invention comprises 20 mg/ml of the VEGF antagonist, 5 mM sodium phosphate buffer, 0.015% polysorbate, 20 mM sodium chloride, and 2.5% sucrose, pH about 6.2-6.3.

[0030] In another embodiment, the lyophilizable ophthalmic formulation comprises 5 mg/ml, 10 mg/ml, or 40 mg/ml VEGF antagonist, 5 mM sodium phosphate buffer, 0.015% polysorbate, 20 mM sodium chloride, and 2.5% sucrose, at pH 6.2-6.3. In a specific embodiment, the lyophilizable ophthalmic formulation consists essentially of 5 mg/ml, 10 mg/ml, or 40 mg/ml VEGF antagonist (SEQ ID NO:4), 5 mM sodium phosphate buffer, 0.015% polysorbate, 20 mM sodium chloride, and 2.5% sucrose, at pH 6.2-6.3.

[0031] In another specific embodiment, the lyophilizable ophthalmic formulation comprises 20 mg/ml of the VEGF antagonist, 5 mM sodium phosphate buffer, 0.015% polysorbate, and 67.5 mM sodium chloride, pH about 6.2-6.3. In a more specific embodiment, the lyophilizable ophthalmic formulation consists essentially of 20 mg/ml of the VEGF antagonist (SEQ ID NO:4), 5 mM sodium phosphate buffer, 0.015% polysorbate, and 67.5 mM sodium chloride, pH 6.2-6.3.

[0032] In another specific embodiment, the lyophilizable ophthalmic formulation comprises 5 mg/ml, 10 mg/ml, or 40 mg/ml VEGF antagonist, 5 mM sodium phosphate buffer, 0.015% polysorbate, and 67.5 mM sodium chloride, pH about 6.2-6.3. In a more specific embodiment, the lyophilizable ophthalmic formulation consists essentially of 5 mg/ml, 10 mg/ml, or 40 mg/ml VEGF

antagonist (SEQ ID NO:4), 5 mM sodium phosphate buffer, 0.015% polysorbate, and 67.5 mM sodium chloride, pH about 6.2-6.3.

[0033] Generally, the reconstituted formulation is about 2 times the concentration of the pre-lyophilized formulation, e.g., a 20 mg fusion protein/ml pre-lyophilized formulation is reconstituted to a final formulation of 40 mg fusion protein/ml.

[0034] Generally, the lyophilized formulation is reconstituted with sterile water suitable for injection. In one embodiment, the reconstitution liquid is bacteriostatic water.

[0035] In another aspect, the invention features a method of producing a lyophilized formulation of a VEGF-specific fusion protein antagonist, comprising subjecting the lyophilizable formulation of the invention to lyophilization to generate a lyophilized formulation. The lyophilized formulation may be lyophilized by any method known in the art for lyophilizing a liquid.

[0036] In another related aspect, the invention features a method of producing a reconstituted lyophilized formulation of a VEGF antagonist, comprising reconstituting the lyophilized formulation of the invention to a reconstituted formulation. In one embodiment, the reconstituted formulation is twice the concentration of the pre-lyophilized formulation, e.g., the method of the invention comprises: (a) producing a pre-lyophilized formulation of a VEGF-specific fusion protein antagonist, (b) subjecting the pre-lyophilized formulation of step (a) to lyophilization; and (c) reconstituting the lyophilized formulation of step (b).

[0037] The invention further features ophthalmic formulations provided in a pre-filled syringe or vial, particularly suitable for intravitreal administration.

[0038] Other objects and advantages will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[0039] The present invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting unless indicated, since the scope of the present invention will be limited only by the appended claims.

[0040] Unless stated otherwise, all technical and scientific terms and phrases used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference.

General Description

[0041] Safe handling and administration of formulations comprising proteins represent significant challenges to pharmaceutical formulators. Proteins possess unique chemical and physical properties that present stability problems: a variety of degradation pathways exist for proteins, implicating both chemical and physical instability. Chemical instability includes deamination, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Physical instability encompasses many phenomena, including, for example, aggregation and/or precipitation.

[0042] Chemical and physical stability can be promoted by removing water from the protein. Lyophilization (freeze-drying under controlled conditions) is commonly used for long-term storage of proteins. The lyophilized protein is substantially resistant to degradation, aggregation, oxidation, and other degenerative processes while in the freeze-dried state. The lyophilized protein may be reconstituted with water optionally containing a bacteriostatic preservative (e.g., benzyl alcohol) prior to administration.

Definitions

[0043] The term "carrier" includes a diluent, adjuvant, excipient, or vehicle with which a composition is administered. Carriers can include sterile liquids, such as, for example, water and oils, including oils of petroleum, animal, vegetable or synthetic origin, such as, for example, peanut oil, soybean oil, mineral oil, sesame oil and the like.

[0044] The term "excipient" includes a non-therapeutic agent added to a pharmaceutical composition to provide a desired consistency or stabilizing effect. Suitable pharmaceutical excipients include, for example, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like.

[0045] The term "lyophilized" or "freeze-dried" includes a state of a substance that has been subjected to a drying procedure such as lyophilization, where at least 90% of moisture has been

removed.

VEGF Antagonists

[0046] A VEGF antagonist is a compound capable of blocking or inhibiting the biological action of vascular endothelial growth factor (VEGF), and includes fusion proteins capable of trapping VEGF. In a preferred embodiment, the VEGF antagonist is the fusion protein of SEQ ID NO:2 or 4; more preferably, SEQ ID NO:4. In specific embodiments, the VEGF antagonist is expressed in a mammalian cell line such as a CHO cell and may be modified post-translationally. In a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID NO:4 and is glycosylated at Asn residues 62, 94, 149, 222 and 308. Preferably, the VEGF antagonist is a dimer composed of two fusion proteins of SEQ ID NO:4.

[0047] The VEGF antagonist of the methods and formulations of the invention can be prepared by any suitable method known in the art, or that comes to be known. The VEGF antagonist is preferably substantially free of protein contaminants at the time it is used to prepare the pharmaceutically acceptable formulation. By "substantially free of protein contaminants" is meant, preferably, that at least 90 % of the weight of protein of the VEGF-specific fusion protein antagonist preparation used for making a formulation is VEGF fusion protein antagonist protein, more preferably at least 95%, most preferably at least 99%. The fusion protein is preferably substantially free of aggregates. "Substantially free of aggregates" means that at least 90% of the weight of fusion protein is not present in an aggregate at the time the fusion protein is used to prepare the pharmaceutically effective formulation. Unless stated otherwise, the phosphates employed are sodium phosphates and a desired buffering pH is achieved by mixing appropriate amounts of mono- and dibasic sodium phosphate.

Stable Liquid Ophthalmic Formulations

[0048] In one aspect, the invention provides a stable pharmaceutically acceptable formulation comprising a VEGF antagonist, wherein the formulation is a liquid formulation suitable for ophthalmic use. Preferably, the liquid formulation comprises a pharmaceutically effective amount of the VEGF antagonist. The formulation can also comprise one or more pharmaceutically acceptable carriers, buffers, tonicity agents, stabilizers, and/or excipients. An example of a pharmaceutically acceptable liquid formulation comprises a VEGF antagonist in a pharmaceutically effective amount, a buffer, an organic co-solvent such as polysorbate, a tonicity agent such as NaCl, and optionally, a

stabilizer such as sucrose or trehalose.

[0049] Stability is determined in a number of ways at specified time points, including determination of pH, visual inspection of color and appearance, determination of total protein content by methods known in the art, e.g., UV spectroscopy, and purity is determined by, for example, SDS-PAGE, size-exclusion HPLC, bioassay determination of activity, isoelectric focusing, and isoaspartate quantification. In one example of a bioassay useful for determining VEGF antagonist activity, a BAF/3 VEGFR1/EPOR cell line is used to determine VEGF165 binding by the VEGF antagonist of the invention.

[0050] Liquid formulations can be stored in an oxygen-deprived environment. Oxygen-deprived environments can be generated by storing the formulations under an inert gas such as, for example, nitrogen or argon. Liquid formulations are preferably stored at about 5°C.

Ophthalmic Lyophilized Formulations

[0051] In one aspect of the invention, an ophthalmically acceptable formulation comprising a VEGF antagonist is provided, wherein the formulation is a lyophilizable formulation. Lyophilizable formulations can be reconstituted into solutions, suspensions, emulsions, or any other suitable form for administration or use. Lyophilizable formulations are typically first prepared as liquids, then frozen and lyophilized. The total liquid volume before lyophilization can be less, equal to, or more than, the final reconstituted volume of the lyophilized formulation. The lyophilization process is well known to those of ordinary skill in the art, and typically includes sublimation of water from a frozen formulation under controlled conditions.

[0052] Lyophilized formulations can be stored at a wide range of temperatures. Lyophilized formulations may be stored below 25°C, for example, refrigerated at 2-8°C, or at room temperature (e.g., approximately 25°C). Preferably, lyophilized formulations are stored below about 25°C, more preferably, at about 4-20°C; below about 4°C; below about -20°C; about -40°C; about -70°C, or about -80°C. Stability of the lyophilized formulation may be determined in a number of ways known to the art, for example, by visual appearance of the cake and/or by moisture content.

[0053] Lyophilized formulations are typically reconstituted for use by addition of an aqueous solution to dissolve the lyophilized formulation. A wide variety of aqueous solutions can be used to reconstitute a lyophilized formulation. Preferably, lyophilized formulations are reconstituted using water. Lyophilized formulations are preferably reconstituted with a solution consisting essentially of

water (e.g., USP WFI, or water for injection) or bacteriostatic water (e.g., USP WFI with 0.9% benzyl alcohol). However, solutions comprising buffers and/or excipients and/or one or more pharmaceutically acceptable carries can also be used.

[0054] Freeze-dried or lyophilized formulations are typically prepared from liquids, that is, from solutions, suspensions, emulsions, and the like. Thus, the liquid that is to undergo freeze-drying or lyophilization preferably comprises all components desired in a final reconstituted liquid formulation. As a result, when reconstituted, the freeze-dried or lyophilized formulation will render a desired liquid formulation upon reconstitution.

EXAMPLES

[0055] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only to the appended claims.

[0056] As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise. Thus for example, a reference to "a method" includes one or more methods, and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

[0057] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

Example 1. Stability of 50 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 3 ml Glass Vials.

[0058] An ophthalmic liquid formulation containing 50 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, 5% sucrose, and pH 6.25, was stored at 5 °C in 3 ml glass vials and samples tested at 3, 6, 9, 12, 18 and 24 months. Stability was determined by SE-

HPLC. The results are shown in Table 1. Turbidity was measured at OD_{405} nm; and percent recovered protein and purity by size exclusion HPLC.

Table 1. Stability of 50 mg/ml VEGF Trap Protein (VGFT-SS065)

Months	Visual Appearance	Turbidity (OD_{405} nm)	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.2	100	98.8
3	Pass	0.00	6.2	101	98.7
6	Pass	0.01	6.3	100	98.3
9	Pass	0.01	6.3	101	98.3
12	Pass	0.01	6.3	104	98.4
18	Pass	0.01	6.3	96	98.1
24	Pass	0.01	6.3	105	98.1

Example 2. Stability of 50 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 3 ml Glass Vials.

[0059] A liquid formulation containing 50 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 50 mM NaCl, 3% polyethylene glycol 3350, 5% sucrose, and pH 6.25, was stored at 5 °C in 3 nil glass vials and samples tested at 3, 6, 9, 12, 18 and 24 months. Stability results are shown in Table 2. Turbidity, percent recovered protein and purity was determined as described above.

Table 2. Stability of 50 mg/ml VEGF Trap Protein (VGFT-SS065)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.2	100	98.9
3	Pass	0.00	6.1	104	98.5
6	Pass	0.01	6.3	99	98.3
9	Pass	0.00	6.3	102	97.6
12	Pass	0.01	6.3	103	98.0
18	Pass	0.00	6.3	113	97.7
24	Pass	0.00	6.2	106	97.6

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		

Example 4. Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in Pre-filled Glass Syringe.

[0061] 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 with 4023/50 FluroTec coated plunger and samples tested at 0.5, 1, 2, 3, and 4 months. Stability results are shown in Table 4. Turbidity, percent recovered protein and purity was determined as described above.

Table 4. 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	99.4
0.5	Pass	0.00	6.3	100	99.3
1	Pass	0.00	6.3	100	99.4
2	Pass	0.00	6.3	97	99.1
3	Pass	0.01	6.4		
4	Pass	0.01	6.3		

Example 5. Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 3 ml Glass Vials.

[0062] A liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 135 mM NaCl, 0.03% polysorbate 20, 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 5. Turbidity, percent recovered protein and purity was determined as described above.

Table 5. Stability of 40 mg/ml VEGF Trap Protein (VGFT-SS203)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.3	100	99.3
0.5	Pass	0.00	6.2	87	99.2
1	Pass	0.00	6.2	88	99.1
2	Pass	0.00	6.3	103	99.2
3	Pass	0.00	6.3	88	99.0
4	Pass	0.00	6.2	85	98.9
5	Pass	0.00	6.3	84	99.0

Example 6. Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 1 ml Pre-filled Glass Syringe.

[0063] A liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 135 mM NaCl, 0.03% polysorbate 20, and pH 6.3, was stored at 5 °C in 1 ml prefilled glass luer syringe with 4023/50 FluroTec coated plunger and samples tested at 0.5, 1, 2, 3, 4, and 5 months. Stability results are shown in Table 6. Turbidity, percent recovered protein and purity was determined as described above.

Table 6. Stability of 40 mg/ml VEGF Trap Protein (VGFT-SS203)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.3	100	99.2
0.5	Pass	0.01	6.3	101	99.2
1	Pass	0.00	6.3	101	99.2
2	Pass	0.00	6.3	-	-
3	Pass	0.01	6.3	102	99.1
4	Pass	0.01	6.3	103	98.8
5	Pass	0.00	6.3	99	98.9

Example 7. Stability of Lyophilized 20 mg/ml VEGF Trap Formulation Stored at 5°C in 3 ml Glass Vials and Reconstituted to 40 mg/ml.

[0064] 0.8 ml of a liquid formulation containing 20 mg/ml VEGF trap (SEQ ID NO:4), 5 mM

phosphate, 20 mM NaCl, 0.015% polysorbate 20, 2.5% sucrose, and pH 6.3, were lyophilized in 3 ml glass vials. Samples were stored at 5°C and tested at 1, and 2 months. VEGF trap was reconstituted to a final concentration of 40 mg/ml VEGF Trap (final volume of 0.4 ml). Stability results are shown in Table 7 (t = time in months; * = visual appearance; **=reconstitution time). Turbidity, percent recovered protein and purity was determined as described above.

Table 7. Stability of Lyophilized 20 mg/ml VEGF Trap Protein (VGFT-SS216)

t	Vis. App.*	Recon. Time** (min)	Vis. App.* Reconst'd Liquid	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Config.
0	Pass	0.6	Pass	0.00	6.3	100	99.5
1	Pass	0.6	Pass	0.01	6.3	106	99.4
2	Pass	0.4	Pass	0.01	6.2	103	99.3

Example 8. Stability of Lyophilized 20 mg/ml VEGF Trap Formulation Stored at 5°C in 3 ml Glass Vials.

[0065] 0.8 ml of a liquid formulation containing 20 mg/ml VEGF trap (SEQ ID NO:4), 5 mM phosphate, 67.5 mM NaCl, 0.015% polysorbate 20, and pH 6.3, were lyophilized in 3 ml glass vials. Samples were stored at 5°C and tested at 1, 2, and 3 months. VEGF trap was reconstituted to a final concentration of 40 mg/ml VEGF trap (final volume of 0.4 ml). Stability results are shown in Table 8 (t = time in months; * = visual appearance; **=reconstitution time).

Table 8. Stability of Lyophilized 20 mg/ml VEGF Trap Protein (VGFT-SS216)

t	Vis. App.*	Recon. Time** (min)	Vis. App. Reconst'd Liquid	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Config.
0	Pass	0.7	Pass	0.00	6.3	100	99.0
1	Pass	0.7	Pass	0.01	6.2	105	98.9
2	Pass	0.4	Pass	0.01	6.2	103	98.9

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	VEGF ANTAGONIST FORMULATIONS FOR INTRAVITREAL ADMINISTRATION

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 13/914,996

filed on June 11, 2013.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

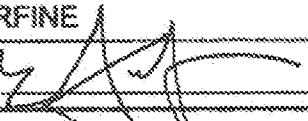
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Eric FURFINE Date (Optional): 30 Jan 2014

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/01 (06-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	VEGF ANTAGONIST FORMULATIONS FOR INTRAVITREAL ADMINISTRATION

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 13/914,996

filed on June 11, 2013.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

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LEGAL NAME OF INVENTOR

Inventor: Daniel DIX Date (Optional): Jan 23, 2014

Signature: Daniel A. Dix

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	VEGF ANTAGONIST FORMULATIONS FOR INTRAVITREAL ADMINISTRATION

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LEGAL NAME OF INVENTOR

Inventor: Kenneth GRAHAM Date (Optional): 19 Feb 2014

Signature: Kenneth B Graham

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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☐ The attached application, or

☒ United States application or PCT international application number 13/914,996

filed on June 11, 2013.

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LEGAL NAME OF INVENTOR

Inventor: Kelly FRYE Date (Optional): 12-16-13

Signature: Kelly J Frye

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronically Filed January 10, 2020

NOTIFICATION OF PRIOR SEQUENCE LISTING		
	Attorney Docket	REGN-024CON10
	First Named Inventor	FURFINE, ERIC
	Application Number	To Be Assigned
Address to: Mail Stop Patent Application Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Filing Date	
	Confirmation Number	To Be Assigned
	Group Art Unit	
	Examiner Name	
	Title: "VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION"	

Sir:

The above-identified patent application contains sequences of nucleic acid and polypeptides. A sequence listing was prepared for parent application, **16/582,486,** filed **September 25, 2019**, in paper and computer-readable format. The sequence information in the paper or compact disk copy of the sequence listing (required by 1.821(c)) of this application is identical to the sequence information in the computer-readable format of the above-identified other application. No new matter has been added. Therefore, please transfer to this application, in accordance with 37 CFR § 1.821(e), the fully compliant computer readable copy from applicants' other application. A paper (.pdf) copy of this sequence listing is enclosed.

Applicants respectfully submit that the present patent application is now in compliance with 37 CFR §§ 1.821 - 1.825. The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number REGN-024CON10.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Dated: January 10, 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, California 94065
Telephone: (650) 327-3400
Direct: (650) 833-7735
Facsimile: (650) 327-3231

SEQUENCE LISTING

<110> Regeneron Pharmaceuticals, Inc.

<120> VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

<130> 5050F

<150> US 13/914,996
<151> 2013-06-11

<150> US 13/329,770
<151> 2011-06-11

<150> US 12/833,417
<151> 2010-07-09

<150> US 12/560,885
<151> 2009-09-16

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atcgacaaac caatacaatc atagatgtgg ttctgagtcc gtctcatgga attgaactat 480

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Petitioner Fresenius Ex. 1004, 0374

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35 40 45

Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr Val Thr Leu
50 55 60

Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile
65 70 75 80

Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu
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Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His Leu Tyr Lys

Petitioner Fresenius Ex. 1004, 0375

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Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe Leu Ser Thr
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Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr Phe Val Arg
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Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
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Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
            260                 265                 270

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
        275                 280                 285

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
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Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
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His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
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Petitioner Fresenius Ex. 1004, 0376

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385 390 395 400

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
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cctaacatca ctgttacttt aaaaaagttt ccacttgaca ctttgatccc tgatggaaaa 240

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catcgacaaa ccaatacaat catagatgtg gttctgagtc cgtctcatgg aattgaacta 420

tctgttggag aaaagcttgt cttaaattgt acagcaagaa ctgaactaaa tgtggggatt 480

gacttcaact gggaataccc ttcttcgaag catcagcata agaaacttgt aaaccgagac 540

ctaaaaaccc agtctgggag tgagatgaag aaatttttga gcaccttaac tatagatggt 600

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Petitioner Fresenius Ex. 1004, 0377

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aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg 960

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aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag 1260

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Cys Leu Leu Leu Thr Gly Ser Ser Ser Gly Ser Asp Thr Gly Arg Pro
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Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
35 40 45

Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
50 55 60

Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
65 70 75 80

Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
85 90 95

Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
100 105 110

Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
115 120 125

Petitioner Fresenius Ex. 1004, 0378

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Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
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Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
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Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
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Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
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Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
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Phe Val Arg Val His Glu Lys Asp Lys Thr His Thr Cys Pro Pro Cys
225                 230                 235                 240

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
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Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
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Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
        275                 280                 285

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
    290                 295                 300

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
305                 310                 315                 320

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
                325                 330                 335

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
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Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
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Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
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Petitioner Fresenius Ex. 1004, 0379

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Petitioner Fresenius Ex. 1004, 0380

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-024CON10
	Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Eric		FURFINE	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Concord	State/Province	MA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	315 Harrington Avenue		
Address 2			
City	Concord	State/Province	MA
Postal Code	01742	Country i	US

Inventor 2

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Daniel		DIX	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	LaGrangeville	State/Province	NY	Country of Residence i	US

Mailing Address of Inventor:

Address 1	55 Memory Trail		
Address 2			
City	LaGrangeville	State/Province	NY
Postal Code	12540	Country i	US

Inventor 3

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Kenneth		GRAHAM	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-024CON10
	Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION	

Residence Information (Select One)	◉ US Residency	○ Non US Residency	○ Active US Military Service		
City	Pleasant Valley	**State/Province**	NY	**Country of Residence** i	US

Mailing Address of Inventor:

Address 1	c/o Regeneron Pharmaceuticals, Inc.		
Address 2	777 Old Saw Mill River Road		
City	Tarrytown	**State/Province**	NY
Postal Code	10591	**Country** i	US

Inventor 4

Legal Name

Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Kelly		FRYE	

Residence Information (Select One)	◉ US Residency	○ Non US Residency	○ Active US Military Service		
City	Mendham	**State/Province**	NJ	**Country of Residence** i	US

Mailing Address of Inventor:

Address 1	3 McVickers Lane		
Address 2			
City	Mendham	**State/Province**	NJ
Postal Code	07945	**Country** i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	96387		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION		
Attorney Docket Number	REGN-024CON10	**Small Entity Status Claimed**	☐
Application Type			
Subject Matter			
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-024CON10
	Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	96387		

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix	Remove
Registration Number					
Prefix	**Given Name**	Middle Name	**Family Name**	Suffix	Remove
Registration Number					

Additional Representative Information blocks may be generated within this form by selecting the **Add** button.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-024CON10
	Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove

Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	16582486	2019-09-25

Prior Application Status	Patented	Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16582486	Continuation of	16159269	2018-10-12	10464992	2019-11-05

Prior Application Status	Patented	Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16159269	Continuation of	15879294	2018-01-24	10400025	2019-09-03

Prior Application Status	Patented	Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15879294	Continuation of	15095606	2016-04-11	9914763	2018-03-13

Prior Application Status	Patented	Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15095606	Continuation of	14330096	2014-07-14	9340594	2016-05-17

Prior Application Status	Patented	Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14330096	Continuation of	13914996	2013-06-11	8802107	2014-08-12

Prior Application Status	Patented	Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13914996	Continuation of	13329770	2011-12-19	8481046	2013-07-09

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-024CON10
	Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION	

Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13329770	Continuation of	12833417	2010-07-09	8092803	2012-01-10

Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
12833417	Continuation of	12560885	2009-09-16	7807164	2010-10-05

Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
12560885	Division of	11818463	2007-06-14	7608261	2009-10-27

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
11818463	Claims benefit of provisional	60814484	2006-06-16

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-024CON10
	Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION	

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-024CON10
	Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-024CON10
	Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:	

If the Applicant is an Organization check here. ☒

Organization Name	REGENERON PHARMACEUTICALS, INC.

Mailing Address Information For Applicant:

Address 1	777 Old Saw Mill River Road		
Address 2			
City	Tarrytown	**State/Province**	NY
Country[i]	US	Postal Code	10591
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-024CON10
	Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION	

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	REGENERON PHARMACEUTICALS, INC.

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	777 Old Saw Mill River Road		
Address 2			
City	Tarrytown	**State/Province**	NY
Country i	US	Postal Code	10591
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

PTO/AIA/14 (08-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-024CON10
	Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION	

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e. g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Karl Bozicevic/			Date (YYYY-MM-DD)	
First Name	Karl	Last Name	Bozicevic	Registration Number	28807

Additional Signature may be generated within this form by selecting the Add button.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Filer:	Karl Bozicevic/Savanna Fuentes
Attorney Docket Number:	REGN-024CON10

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	300	300
UTILITY SEARCH FEE	1111	1	660	660
UTILITY EXAMINATION FEE	1311	1	760	760
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1720**

Electronic Acknowledgement Receipt

EFS ID:	38262200
Application Number:	16739559
International Application Number:	
Confirmation Number:	1153
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-024CON10
Receipt Date:	10-JAN-2020
Filing Date:	
Time Stamp:	14:00:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1720
RAM confirmation Number	E202010E01055057
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		REGN-024CON10_2020-01-10_prelim_amend.pdf	58009 fedf242c1e4da38f9d8d3a8019117107c8a280ab	yes	5

Multipart Description/PDF files in .zip description

Document Description	Start	End
Applicant Arguments/Remarks Made in an Amendment	4	5
Claims	2	3
Preliminary Amendment	1	1

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
2		REGN-024CON10_appln.pdf	766509 8daf0d517068c168f5c827e98848eb344ea0df38	yes	16

Multipart Description/PDF files in .zip description

Document Description	Start	End
Abstract	16	16
Claims	15	15
Specification	1	14

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
3	Oath or Declaration filed	REGN-024CON10_declaration.pdf	551390 8a857f03087a869974574de3cf74617f361f334f	no	4

Warnings:

Information:

4	Sequence Listing	REGN-024CON10_2020-01-10_seq_list_trans.pdf	27666 ab41ad53a8f61b5746f5e86d8b527cdb8cfc3937	no	1
Warnings:					
Information:					
5	Sequence Listing	REGN-024CON10_seq_list.pdf	181040 4a3a95a26c9d81af7c0116a5a4962deb6916ae54	no	7
Warnings:					
Information:					
6	Application Data Sheet	WebADS.pdf	185394 0caa0357d4d5f6384330aee687364e86a3ba5e2d	no	10
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	34817 0a625ddd2eb42a4b4f90301b8b3a0a417f84e556	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1804825		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REMARKS UNDER 37 CFR § 1.115

Formal Matters

Claims 1-9 are now pending in this application.

The original claims have been cancelled without prejudice.

New claims 1-9 are fully supported within the originally filed application. Specific support can be found in original paragraph [0037] and in example 6.

The claims 1-9 correspond to claims 1-9 of issued U.S. Patent 10,464,992 except that the claims of this application relate to a "pre-filled syringe" as opposed to the --vial—referred to within the '992 patent.

No new matter has been added.

Statement under 37 C.F.R. §§1.56 and 1.2

Applicant(s) hereby advise the Examiner of the status of a co-pending application in compliance with the Applicant's(s') duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

Applicants wish to bring to the Examiner's attention co-pending U.S. Patent Application No. 16/159,269, filed October 12, 2018. No actions have been mailed to date.

Applicants wish to bring to the Examiner's attention U.S. Patent Nos. 7,608,261; 8,092,803; 8,481,046; 8,802,107; 9,340,594; 9,914,763; 9,580,489; 7,807,164; and 10,464,992 which are all issued patents to which the above-referenced patent application claims priority.

This document is (These documents are) available on PAIR, and thus is (are) not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the document(s) from PAIR.

Petitioner Fresenius Ex. 1004, 0396

CONCLUSION

Applicant(s) submit(s) that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-024CON10.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: January 10, 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Petitioner Fresenius Ex. 1004, 0397

AMENDMENTS TO THE CLAIMS

1. (**New**) A pre-filled syringe comprising: a vascular endothelial growth factor (VEGF) antagonist, an organic co-solvent, a buffer, and a stabilizing agent, wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5°C for two months as measured by size exclusion chromatography.

2. (**New**) The pre-filled syringe of claim 1, wherein about 99% or more of the weight of the fusion protein is in native conformation.

3. (**New**) The pre-filled syringe 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.

4. (**New**) The pre-filled syringe of claim 3, wherein the fusion protein comprises amino acids 27-457 of SEQ ID NO:4.

5. (**New**) The pre-filled syringe of claim 4, wherein the VEGF antagonist is a dimer of the fusion protein.

6. (**New**) The pre-filled syringe 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.

7. (**New**) The pre-filled syringe of claim 6, wherein the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.

8. (**New**) The pre-filled syringe of claim 1, wherein the organic co-solvent is polysorbate 20 and the stabilizing agent is sucrose.

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9. (**New**) The pre-filled syringe of claim 1, wherein the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose.

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