UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case PGR2021-TBA
Patent No. 10,857,231

PETITION FOR POST-GRANT REVIEW OF U.S. PATENT NO. 10,857,231 UNDER 35 U.S.C. §§ 321-329 AND 37 C.F.R. § 42.200 ET SEQ.

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1069	Terry Riss et al., "Choosing the Right Cell-Based Assay for Your Research," *Cell Notes*, 6:6-12 (2003)
1070	Terry Riss and Richard A. Moravec, "Use of Multiple Assay Endpoints to Investigate the Effects of Incubation Time, Dose of Toxin, and Plating Density in Cell-Based Cytotoxicity Assays," *ASSAY and Drug Development Technologies*, 2(1):51-75 (2004)
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1076	Notice of Allowance, filed on Dec. 19, 2011, in U.S. Patent Application No. 12/835,065
1077	Torben Laursen et al., "Pain Perception after Subcutaneous Injections of Media Containing Different Buffers," *Basic & Clinical Pharmacology & Toxicology*, 98:218-221 (2006)

Prosecution history exhibits do not include prior art references. All exhibits are cited in this Petition using page numbers added by Petitioner.

I. INTRODUCTION

Celltrion, Inc. ("Petitioner") respectfully requests institution of a post-grant review ("PGR") of claims 1-11, 17-21, 27-32, 41-53, and 58-67 (the "Challenged Claims") of U.S. Patent No. 10,857,231 ("the '231 patent"). The '231 patent issued from U.S. 16/535,610 ("the '610 application"), filed August 8, 2019, and identifies Regeneron Pharmaceuticals, Inc. ("Regeneron" or "PO") as assignee.

The Challenged Claims are directed to extremely broad genera of formulations comprising VEGF antagonist fusion proteins ("VEGF Trap") with broadly defined excipients, which are not limited in concentration in at least the independent claims. The claimed formulations are primarily defined by their function, *i.e.*, by what they do, not what they are—specifically, the ability of the formulation to maintain the stability, potency, or binding of the VEGF Trap.

Despite the wide breadth of the claims, the specification contains little disclosure related to the claimed formulations. The '231 patent describes five different "aspects" or alleged inventions—none of which corresponds to the claimed formulations. Perhaps most surprising, the specification fails to include even a single representative species within the scope of any Challenged Claim. Even when data are included in the specification (for other formulations outside the scope of the claims), the data demonstrate that certain of those formulations do ***not*** exhibit the claimed functional properties. The extremely limited—and

oftentimes contradictory—disclosure in the specification does not demonstrate that the inventors were in possession of the broadly claimed formulations. Thus, the Challenged Claims lack adequate written description.

Similarly, the lack of disclosure in the specification evidences that POSAs would have needed to engage in undue experimentation to practice the full scope of the claims. Indeed, simply making the full scope of the claimed formulations, without regard to the claimed functional properties, would require undue experimentation, as the claims encompass numerous (nearly 5 million by conservative estimates), uncommon, and difficult-to-develop formulations. Making and screening the full scope of these claimed formulations for the recited functionalities would require the exact type of trial-and-error testing that the case law rejects. Thus, the Challenged Claims also are not enabled.

Further, POSAs would not have been able to determine whether or not a given formulation was within the scope of the claims. Each Challenged Claim includes a functional property (stability, potency, or binding affinity), which can all be measured using various techniques that can yield significantly different results. Yet, the ’231 patent fails to provide the requisite guidance on which methodology to use, and the claims fail to specify the methodology to determine whether the claim limitations are satisfied. Moreover, the ’231 patent includes data indicating that the very same formulation sometimes possesses the claimed

functionality and sometimes does not, after only a mere matter of hours. Thus, the Challenged Claims are indefinite.

PO may assert in response that the limited disclosure is sufficient to satisfy the requirements of 35 U.S.C. §§ 112 (a) and (b)—that is, the '231 patent does provide sufficient written description, enable POSAs to make and use the full scope of claimed formulations without undue experimentation, and that the claims are definite under § 112(b). Any such arguments, if accepted, would compel a conclusion that the Challenged Claims are invalid as obvious under § 103, because the '231 patent specification does not provide any additional information for VEGF Trap formulations that was not already taught by the prior art. Two of PO's own prior art publications, Wulff and Fraser, disclose VEGF Trap formulations comprising the same excipients at the same concentrations disclosed in the examples of the '231 patent (*i.e.*, phosphate/citrate buffer, polysorbate, and sucrose). While the formulations disclosed in Wulff and Fraser used a phosphate/citrate buffer, whereas the Challenged Claims recite buffers comprising histidine, POSAs would have been strongly motivated to use a histidine buffer in such a formulation in view of the prior art, including Andya.

Accordingly, for these and the reasons more fully described below, Petitioner respectfully requests institution of a PGR of the '231 patent's Challenged Claims.

II. MANDATORY NOTICES (37 C.F.R. § 42.8)

A. Real Parties-in-Interest

The real parties-in-interest are Celltrion, Inc., Celltrion Healthcare Co. Ltd., and Celltrion Healthcare U.S.A., Inc.

B. Related Matters

The following pending U.S. applications claim the benefit of the ’231 patent: 16/950,584; 17/307,240; 17/308,801; 17/313,627; 17/314,992.

To Petitioner’s knowledge, the ’231 patent is not currently involved in any other judicial or administrative matters that would affect, or be affected by, a decision in this proceeding.

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D. Power of Attorney

A power of attorney is filed herewith according to 37 C.F.R. § 42.10(b).

III. PAYMENT OF FEES (37 C.F.R. § 42.203)

Petitioner submits herewith the fees set forth in 37 C.F.R. § 42.15(b) and authorizes the PTO to charge any required fees, including any excess claim fees, to Deposit Account **02-2135.**

IV. REQUIREMENTS FOR POST-GRANT REVIEW (37 C.F.R. § 42.204)

A. Grounds for Standing (37 C.F.R. § 42.204(a))

The ’231 patent is available for PGR, and Petitioner is not barred or estopped from requesting PGR on grounds identified in this Petition. Neither Petitioner nor its privies own the ’231 patent; nor has it filed a U.S. civil action challenging validity of any claim of the ’231 patent.

Although the ’231 patent claims priority to applications filed before the AIA’s effective date, it is eligible for PGR pursuant to AIA, § 3(n)(1) because the granted claims, including all Challenged Claims, do not have Section 112 support in any of the pre-AIA applications as explained in Sections X, XI.A, and XI.B, below.

This Petition is filed no more than nine months after issuance of the '231 patent. *See* 35 U.S.C. § 321(c).

B. Identification of Challenged Claims and Specific Statutory Grounds (37 C.F.R. § 42.204(b)(1)-(2))

Petitioner challenges Claims 1-11, 17-21, 27-32, 41-53, and 58-67 of the '231 patent ("the Challenged Claims").

The specific statutory grounds for the challenge are as follows:

Ground	Claims	Statutory Basis	Prior Art
Ground 1	1-11, 17-21, 27-32, 41-53, and 58-67	35 U.S.C. § 112(a) Lack of Written Description	
Ground 2	1-11, 17-21, 27-32, 41-53, and 58-67	35 U.S.C. § 112(a) Lack of Enablement	
Ground 3	1-11, 17-21, 27-32, 41-53 and 58-67	35 U.S.C. § 112(b) Indefiniteness	
Ground 4	1-4, 6-11, 18-21, 27-32, 41-45, 58-59	35 U.S.C. § 103	Wulff (Ex. 1004) or Fraser (Ex. 1003) in view of Andya (Ex. 1005)

V. BACKGROUND AND SUMMARY OF THE '231 PATENT

The '610 application was filed on August 8, 2019, and issued as the '231 patent on December 8, 2020. Ex. 1002, ¶74. It was a continuation application and claims priority to seven patents and two abandoned applications, all of which share a common specification and are continuations or divisionals of U.S. 11/387,256, filed on March 22, 2006. *Id.* ¶¶99-100. The '231 patent claims priority to

provisional 60/665,125, but it lacks copious disclosures that were later added to the common specification, as shown in Ex. 1008. *See also* Ex. 1002, ¶¶90, 96.

The '231 patent is directed to stable formulations of a VEGF Trap. Ex. 1002, ¶75; Ex. 1001, 1:65-2:3. Independent claims 1, 27, and 31 are directed to broad genera of VEGF Trap formulations including the same excipients, differing only in their wherein clauses. *See id.* ¶¶165-66. Each of the claims recites formulations comprising: (a) 10-50 mg/ml VEGF Trap, (b) a buffer comprising histidine; (c) an organic co-solvent comprising polysorbate; and (d) a stabilizing agent comprising a sugar, an amino acid or both. Ex. 1002, ¶165; Ex. 1001, 19:34-45, 20:64-21:9, and 21:18-29. The claims contain no pH limitations. The only differences lie in the claims' wherein clauses, which recite:

> 1. "wherein said VEGF antagonist fusion protein exhibits less than about 3% degradation after 15 months of storage at 5° C."
>
> 27. "wherein said VEGF antagonist fusion protein is capable of inhibiting biological activity of human VEGF as measured by a mouse Baf/3 VEGFRl/EpoR cell line and achieving a percent relative potency of at least 75 relative to a reference VEGF IC_{50} standard."
>
> 31. "wherein said VEGF antagonist fusion protein is capable of binding VEGF at a percent relative binding of at least 88 relative to a reference VEGF IC_{50} standard, after storage at 5° C. for 3 months."

Ex. 1002, ¶166; Ex. 1001, 19:43-45, 21:5-9, 21:26-29.[1]

The '231 patent specification discloses several different alleged "aspects", including three different genera of formulations. Ex. 1002, ¶¶80-83. However, as illustrated below and discussed in Section XI.A.2.a., none of these formulations corresponds to the claimed genera of formulations. *Id.*

'231 Patent Claims	**First "Aspect"**	**Second "Aspect"**	**Third "Aspect"**
A formulation comprising:	Limited to a liquid formulation	Limited to a liquid formulation	Limited to a pre-lyophilized formulation and reconstituted formulation
10-50 mg/ml VEGF Trap	10-50 mg/ml VEGF Trap	50-100 mg/ml VEGF Trap	5-75 mg/ml or 12.5 to 75 mg/ml VEGF Trap
A buffer comprising histidine	Phosphate and/or citrate buffer	1-50 mM histidine buffer	5-50 mM histidine; 10 mM histidine (pre-lyophilized) and 20 mM (after reconstitution)
An organic co-solvent comprising polysorbate	Polysorbate "may be present," but it does not disclose "an organic co-solvent comprising polysorbate"	While the formulation may contain 0.1-0.5% polysorbate or 1-5% PEG, it does not disclose "an	0.1 – 3.0 % PEG (pre-lyophilized)

[1] Claim 1's "wherein" clause is referred to herein as the "stability limitation." Claim 27's "wherein" clause is referred to herein as the "potency limitation." Claim 31's "wherein" clause is referred to herein as the "binding limitation."

’231 Patent Claims	First “Aspect”	Second “Aspect”	Third “Aspect”
		organic co-solvent comprising polysorbate”	as an organic co-solvent[2]
A stabilizing agent comprising a sugar, an amino acid or both	A thermal stabilizer of NaCl and/or sucrose	5-30% sucrose and 25-150 mM NaCl	At least one of 0.25-30.% glycine or 0.5-6.0% sucrose as a lyoprotectant

Ex. 1002, ¶103.

Similarly, the patent specification includes five different examples, none of which is within the scope of the Challenged Claims. Ex. 1002, ¶¶84-86; Ex. 1001, 7:63-12:30. The formulations in Examples 1-3 and one of the formulations in Example 5 do not contain histidine. *Id.* ¶84; Ex. 1001, Examples. As set forth below, the remaining formulations in Examples 4 and 5 are also outside the scope of the claims. *See id.* ¶¶84-86.

[2] While the third aspect includes optionally polysorbate in an amount of 0.003-0.005% (or less than or equal to 0.0005%), it is not disclosed as a component of an organic co-solvent. *See* Ex. 1002, ¶181.

'231 Patent Claims	**Example 4 (10:15-25)**	**Example 4 (10:27-30)**	**Example 5 (10:59-66)**
A formulation comprising:	A pre-lyophilized and reconstituted[3] formulation	A liquid formulation	A pre-lyophilized and reconstituted formulation
10-50 mg/ml of a vascular endothelial growth factor (VEGF) antagonist fusion protein comprising amino acids 27-457 of SEQ ID NO: 4	50 mg/ml VEGF Trap	50, 75, or 100 mg/ml VEGF Trap	50 mg/ml VEGF Trap
a buffer comprising histidine	10 mM histidine	10 mM histidine	10 mM histidine
an organic co-solvent comprising polysorbate,	Not present	Not present (0.1% polysorbate 20 or TY° PEG 3350)[4]	Not present
a stabilizing agent comprising a sugar, an amino acid or both,	0.75% glycine, 2.5% sucrose	5-20% sucrose	2.5% sucrose, 0.75% glycine

Only one formulation (in Example 4) includes both histidine and polysorbate, but it does not include "an organic co-solvent comprising

[3] The concentrations identified in Examples 4 and 5 are for the pre-lyophilized formulation, and those concentrations are doubled when reconstituted.

[4] While certain formulations include polysorbate 20, those formulations do not include an organic co-solvent. Ex. 1002, ¶233; Ex. 1026, 209.

polysorbate" as required by the Challenged Claims, as the example does not comprise an organic co-solvent. *Id.* ¶¶85, 178.

Moreover, the only stability data provided for this example formulation are "% Degradation" as determined by SE-HPLC (size exclusion HPLC). Ex. 1002, ¶¶85, 263; Ex. 1001, 10:38-55. SE-HPLC, however, measures only a portion of protein degradation, and thus, these data are incomplete and fail to provide a complete measure of the percent of protein degradation in the formulation. *See id.*

No potency or binding affinity data are provided for this formulation. *See id.* ¶201. Rather, the only potency and binding data are provided in Example 5, which tested formulations falling outside the Challenged Claims' scope. *See id.* ¶86. Thus, when considered in connection with each "wherein" clause of independent claims 1, 27, and 31, ***there is not even one example that falls within the scope of any claim***. *See id*. ¶¶84-86.

VI. PROSECUTION OF THE '231 PATENT

The originally filed '610 application included 20 claims directed to a completely different alleged invention. Specifically, the original claims recited a mammalian cell comprising a polynucleotide and a method of manufacturing a VEGF Trap. Ex. 1006, 262-63.

After two preliminary amendments and in response to a third-party submission under 37 C.F.R. § 1.290, (*Id.* at 133-182, 196-97, 227-28), PO

submitted a third Preliminary Amendment on June 19, 2020, cancelling all previous claims and adding new claims 49-89 directed to formulations and methods of manufacturing a liquid formulation. *Id.* at 122-26. Each of the six independent claims recited a formulation or a method of manufacturing a formulation comprising 10-50 mg/ml VEGF Trap, a buffer, an organic co-solvent, and a stabilizing agent. *See id.*

The Examiner rejected claims 49-89 under 35 U.S.C. § 112(a) for lack of written description, stating that the specification only discloses three specific formulations, rather than the full breadth of those encompassed by the pending claims. *Id.* at 87-90 (Non-Final Rejection, Sept. 9, 2020). Additionally, the Examiner rejected claims 49-57, 59-65, 76-89 on the grounds of non-statutory double patenting over several other patents and applications. *Id.* at 90-97. The Examiner also determined that the potency limitation claims were not entitled to the priority date of the provisional application. *Id.* at 87.[5]

[5] While the Examiner's finding was likely based on the addition of new matter in the non-provisional, including the Examples, all of the Challenged Claims added new matter, not just those reciting potency limitations. *See* Ex. 1002, Section VI.C. Moreover, as discussed in Sections X and XI.A-B, the Challenged Claims

On October 12, 2020, after an Examiner Interview, (*id.* at 54, 28-29), PO amended the independent claims to recite a buffer comprising histidine, an organic co-solvent comprising polysorbate, and a stabilizing agent comprising a sugar, an amino acid, or both. *Id.* at 41. PO alleged that a person of ordinary skill in the art ("POSA") would have understood that PO was in possession of the claimed formulations, and that all claims recite elements not encompassing an invention that would be obvious in view of any previously-issued patents in the family. *Id.* at 38-39. PO additionally admitted that at least the stability limitation is limiting—stating that the "invention is a formulation which comprises the VEGF antagonist ***and exhibits less than a 3% degradation after 15 months of storage at 5ºC.***" *Id.* at 54 (emphasis added).

On November 2, 2020, the Examiner withdrew the double patenting rejection and issued a Notice of Allowance. *Id.* at 12-19.

VII. LEVEL OF SKILL IN THE ART

The education and experience of a POSA who would have been asked to design a pharmaceutical formulation, such as the claimed formulations of the '231

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are also not entitled to priority of the non-provisional filing date because these claims are not supported by the common specification.

patent, would have had an advanced degree in biology, biochemistry, pharmaceutics, or a related discipline. Ex. 1002, ¶108. The POSA also would have had at least two years of experience in the development and manufacture of formulations of therapeutic proteins. Ex. 1002, ¶¶108, 240.

VIII. THE BOARD SHOULD NOT DENY INSTITUTION UNDER §325(d)

A two-part framework is used to determine if discretionary denial under § 325(d) is appropriate: (1) whether the same or substantially the same art or arguments were previously presented to the PTO, and (2) if either condition of (1) is met, "whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims." *See Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, No. IPR2019-01469, Paper 6 at 8-9 (P.T.A.B. Feb. 13, 2020); *see also* 35 U.S.C. § 325(d). An analysis of both factors shows that a § 325(d) denial is not warranted here.

First, the Examiner did not expressly consider lack of enablement or indefiniteness of the challenged claims, much less the specific arguments raised in this Petition. *Adello Biologics, LLC v. Amgen Inc.*, No. PGR2019-00001, Paper 13 at 10-11 (P.T.A.B. Apr. 19, 2019). Thus, these issues were not considered by the USPTO.

Second, while the Examiner issued a written description rejection, the Examiner did not consider whether there was adequate written description for the

now-claimed histidine-buffered formulations. Ex. 1006, 87-90. At the time of the rejection, the pending claims recited any buffer, organic co-solvents, and stabilizing agents. *See id.* The Examiner noted only that three formulations were disclosed, and these were not representative of the full scope of the claims:

> (1) SS065- 10 mM phosphate, 50 mM NaCl, 0.1 % polysorbate 20, 20% sucrose, and 50 mg/ml VEGF fusion protein (SEQ ID NO:4), pH 6.25- and FS405;
>
> (2) SS101- 50-100 mg/ml VEGF fusion protein (SEQ ID NO:4), 10 mM histidine, 50 mM NaCl, 5-20% sucrose, and one of 0.1 % polysorbate 20 or 3% of PEG 3350;
>
> (3) FS-405- 25 mg/ml VEGF fusion protein (SEQ ID NO:4), 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1 % polysorbate 20, 20% sucrose, pH 6.0-6.1.

See id.

The claims were later amended to recite a histidine buffer, an organic co-solvent comprising polysorbate, and a stabilizing agent comprising sugar, an amino acid, or both. *See id.* at 58-70. The Examiner did not expressly address whether these combination of excipients—with the claimed functional properties—were each sufficiently disclosed to satisfy the written description requirement.

Further, the Examiner materially erred in understanding the scope of the disclosure and breadth of the issued claims. In particular, the Examiner either did not consider whether, or materially erred in concluding that, any of the above-described formulations were within the scope of the claims. The first and third

formulations do not include histidine as required by the claims, and the second example does not include "an organic co-solvent comprising polysorbate." Ex. 1006, 89-90. Indeed, none of the excipients in the second example is an organic co-solvent. Ex. 1002, ¶228. Additionally, the Examiner appears to have overlooked or materially erred in failing to recognize that the concentration of VEGF Trap in the second example only overlapped the claimed range at a single concentration (50 mg/ml). Ex. 1002, ¶¶175, 181.

Moreover, while the Examiner stated that "the instant specification discloses only a few exemplary formulation[s] that are consistent with the stability limitations claimed" in the Non-final Rejection, (Ex. 1006, 90), he either did not consider, or materially erred in concluding, that the specification discloses that the Challenged Claims satisfy the claimed stability limitations. Ex. 1002, ¶¶88-92, 182-192. As discussed below, the specification fails to establish that the claimed formulations exhibit the claimed stability, potency, or binding affinity.

Third, an analysis of the *Becton Dickinson* factors with respect to the prior art-based grounds raised in this Petition demonstrates that a discretionary denial is inappropriate here. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, No. IPR2017-01586, Paper 8 at 17-18 (P.T.A.B. Dec. 15, 2017) (reciting non-exclusive factors (a)-(f) for consideration under § 325(d)).

Wulff and Andya were not cited, much less considered, during prosecution of the ’231 patent. Wulff, a Regeneron VEGF publication, admits that the VEGF Trap, its detailed molecular structure (amino acid sequence), and how it was created were all published in 2000 in PO’s PCT Patent Publication No. WO 2000/075319 A1. Ex. 1002, ¶¶282-294; Ex. 1004, 2798, n.1. Wulff also provides experimental results that were not provided in Fraser and materially differs by disclosing subcutaneous administration, which further motivates use of histidine buffer to avoid pain and reduce osmolality. Ex. 1002, ¶¶153, 291-293, 355; Ex. 1004, 2798. Wulff also materially differs by disclosing a different concentration of VEGF TrapR1R2 according to good practice (12.5 mg/ml or as low as 5 mg/ml at maximal dose volume), motivating use of Andya’s disclosures to generate a higher protein concentration formulation that is particularly useful for subcutaneous administration. *Id*. ¶¶292, 354. Finally, Wulff was published in 2002, which is more than one year before the earliest alleged priority date of the ’231 patent, whereas Fraser was first published on November 23, 2004, which is less than one year prior to that date. *Compare* Ex. 1004 *with* Ex. 1003; Ex. 1002, ¶283, 296.

While a related Andya patent (U.S. Patent No. 6,267,958), as well as Fraser, were listed in an IDS in the ’231 patent prosecution, along with dozens of other references, there is no indication in the record that the Examiner understood their significance. The Examiner erred by not applying these references in any rejection.

Ex. 1006, 188-190. The Examiner also examined related applications to the '231 patent, which claimed phosphate-citrate buffered formulations, including U.S. Patent App. 12/835,065 (which issued as US Patent No. 8,110,546 and is the first issued patent in the '231 patent's priority chain). Ex. 1055. During prosecution of the '065 application, PO submitted a § 1.131 Declaration ("Dix '546") to antedate Fraser. Ex. 1054. In the Notice of Allowance, the Examiner stated that "[Dix '546] presented factual evidence that the invention claimed in the instant Application was completed before the publication date of November 23, 2004 of the reference [Fraser]."[6] Ex. 1076, 7. Thus, while Fraser was in the IDS during prosecution of the '231 patent, it is unclear whether the Examiner accorded it prior art status. The lack of express evaluation of these references (or any others) weighs against a discretionary denial under *Becton Dickinson* factors (a), (b), and (c). As these references were never expressly evaluated, there is no overlap

[6] Importantly, the pending claims of the '065 application were directed to phosphate-citrate buffered formulations, and the data of the Dix '546 relate solely to phosphate-citrate buffered formulations, not the histidine-buffered formulations of the '231 patent. Thus, this declaration is insufficient to antedate Fraser with respect to the Challenged Claims. *See In re DeBaun*, 687 F.2d 459, 462 (C.C.P.A. 1982).

between the arguments made in this Petition and those raised during examination, and factors (d) and (e) further weigh against a discretionary denial.

Finally, with respect to all Grounds in this Petition, the Examiner did not have the evidence presented in connection herewith, including the expert declaration of Dr. Tarantino ("Tarantino Declaration," Ex. 1002), which further weighs against a § 325(d) denial. *See, e.g.*, *Guardian Indus. Corp. v. Pilkington Deutschland AG*, No. IPR2016-01635, Paper 9 at 9-10 (P.T.A.B. Feb. 15, 2017).

As discussed in Section XI below, and detailed in the Tarantino Declaration, the Examiner erred in a manner material to patentability of the Challenged Claims, and thus both conditions of *Advanced Bionic's* two-part framework are met, making a § 325(d) discretionary denial inappropriate.

IX. CLAIM CONSTRUCTION

In a PGR, claims are construed in accordance with the ordinary and customary meaning of such claims as understood by a POSA at the time of invention and in view of the specification and prosecution history pertaining to the patent. 37 C.F.R. § 42.200(b); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*). Unless otherwise addressed in this section, this Petition uses the ordinary and customary meaning for remaining claim terms.

A. "Formulation"

The term "formulation" should be given its ordinary and customary meaning. As described throughout the specification, the term "formulation" includes any type of formulation without limitation. Ex. 1002, ¶159. The specification expressly contemplates "liquid and freeze-dried, or lyophilized formulations," including "lyophilized formulations [that] can be reconstituted into solutions, suspensions, emulsions, or any other suitable form for administration or use." Ex. 1002, ¶159; Ex. 1001, 2:2-3, 6:10-12, Abstract. Likewise, the Examples include liquid and lyophilized formulations. Ex. 1002, ¶159; Ex. 1001, 10:4-26. Thus, a POSA would have understood that the term "formulation" is not limited to any particular type of formulation. *Id.*

B. "Organic Co-solvent Comprising Polysorbate"

The phrase "organic co-solvent comprising polysorbate" appears in every Challenged Claim and should be construed to mean that the claims require an organic co-solvent which includes polysorbate. Ex. 1002, ¶160. When the claim language is unambiguous, as is the case here, it controls. *Straight Path IP Grp., Inc. v. Sipnet EU S.R.O.*, 806 F.3d 1356, 1361 (Fed. Cir. 2015). While the claim is open-ended and includes additional organic co-solvents, the plain language of the Challenged Claims specifies that the organic co-solvent comprises polysorbate, thus the polysorbate is at least one component of the organic co-solvent. *See*

Georgia-Pacific Corp. v. U.S. Gypsum Co., 195 F.3d 1322, 1327-28 (Fed. Cir. 1999). Further, the Federal Circuit has repeatedly explained that claim terms should not be redrafted to render them operable or valid. *Chef Am., Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1373 (Fed. Cir. 2004).

C. "A Sugar"

The term "sugar" appears in independent claims 1, 27, and 31, and a POSA would have understood the term to mean a sugar or alcohol sugar. Ex. 1002, ¶161. Dependent claims 11, 21, 53, and 66 recite that "said sugar is selected from [a] group consisting of dextrose, ribose, fructose, mannitol, inositol, sorbitol, trehalose, sucrose, and lactose." *Id.* A POSA would have understood that this list of "sugars" included alcohol sugars such as mannitol, inositol, and sorbitol. Ex. 1002, ¶161; Ex. 1001, 5:11-16.

D. The "Wherein" Clauses

The "wherein" clauses of claims 1, 27, and 31 should be construed as limiting. A "wherein" clause is limiting where it gives "meaning and purpose" to the claim. *Griffin v. Bertina*, 285 F.3d 1029, 1033-34 (Fed. Cir. 2002); *see also Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1377 (Fed. Cir. 2019). Here, the specification repeatedly refers to the invention as being directed to "stable" formulations, and the wherein clauses give meaning to that stability. *See, e.g.*, Ex. 1001, Abstract, 1:39-40, 1:65-66, 7:22-32.

Moreover, PO admitted during prosecution that at least claim 1's wherein clause is limiting by stating that the recited functionality is a critical part of the invention. Specifically, PO argued that the "***invention*** is a formulation which comprises the VEGF antagonist ***and exhibits less than a 3% degradation after 15 months of storage at 5ºC.***" Ex. 1006, 54 (emphasis added). Thus, PO has admitted that the wherein clauses provide meaning and purpose, and they should be construed as limiting.

E. "Said VEGF Antagonist Fusion Protein Exhibits Less Than About 3% Degradation"

To the extent it could be construed (*see* Secion XI.C), the claim term "degradation" as recited in claim 1 should be given its ordinary and customary meaning and construed to include any and all forms of protein degradation. Ex. 1002, ¶162. Claim 1 recites that the "VEGF antagonist fusion protein exhibits less than about 3% degradation" without limitation to the type of degradation. *Id.* A POSA would have understood that there were many different forms of degradation, and the specification discloses numerous types of chemical and physical instability. Ex. 1002, ¶162; Ex. 1001, 4:37-44. The specification further provides that "[c]hemical instability includes deamination, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Physical instability encompasses many phenomena, including, for example, aggregation." *Id.* Thus, the term "degradation" as used in claim 1 encompasses any form of protein degradation. *Id.*

F. "Tonicity Agent"

The claim term "tonicity agent" is recited in claims 6, 7, 18, 19, 47, 48, 61, and 62. Tonicity agent does not appear in the specification, and thus, POSAs would not have understood it to have any special meaning provided by PO. Ex. 1002, ¶163. Instead, POSAs would have understood that "tonicity agent" has it ordinary and customary meaning, which is "excipients used to adjust the tonicity of a formulation." *Id.*

X. THE '231 PATENT IS ELIGIBLE FOR PGR BECAUSE AT LEAST ONE CLAIM HAS AN EARLIEST EFFECTIVE FILING DATE AFTER MARCH 16, 2013

A. '231 Patent Chain of Priority

The '231 patent is a "transitional" application because it was filed after the March 16, 2013 effective date of the AIA but claims priority to an application filed before that date. It is a continuation in a long line of U.S. non-provisional patent applications spanning more than 15 years since the provisional application was filed. Ex. 1001 (Related U.S. Application Data); Ex. 1002, ¶74. The non-provisional applications share a common specification. *Id.* The non-provisional application also includes additional matter that was not disclosed in the provisional application, including subject matter relating to the "second aspect of the invention" (*e.g.*, Ex. 1001, 2:35-49) and the Examples (*i.e.*, Examples 1-5). Ex. 1002, ¶¶90-92; Ex. 1008 (redline comparison of the non-provisional and provisional applications).

B. At Least Claims 27, 30, and 47 Are Not Entitled to an Effective Filing Date Before March 16, 2013[7]

If a patent contains at least one claim with an effective filing date after March 16, 2013, then the post-grant provisions of the AIA apply. AIA, §§3(n)(1), 6(f)(2)(A). In order for a patent application to be entitled to a "right of priority" or "an earlier filing date" based upon an earlier filed application, the earlier filed application must have disclosed the invention "in the manner provided by section 112(a) (other than the requirement to disclose the best mode)." 35 U.S.C. § 119(e)(1); 35 U.S.C. § 120.

At least claims 27, 30, and 47 of the '231 patent are not entitled to an effective filing date before March 16, 2013, and thus, the '231 patent is eligible for PGR. The '610 application underlying the '231 patent was filed on August 8, 2019, but, as noted above, claims priority to a series of continuation applications (which are substantively the same except for their claims) reaching back to March 22, 2006, as well as a provisional application filed on March 25, 2005. Ex. 1002,

[7] While Petitioner does not address all Challenged Claims in this section for concision, none is entitled to an effective filing date before March 13, 2013, because they all lack § 112 support in the non-provisional and provisional applications (and originally filed claims of any priority application). *See infra* Sections XI.A-B; Ex. 1002, Sections VI.C-D.

¶74. However, the '231 patent's claims are not described or enabled by any of the priority applications or their original claims, all of which are directed to the aspects of the invention recited in the common specification. *See* Sections XI.A-B; *see also* Ex. 1002, Section VI.C and D; Exs. 1059-1067. The aspects of the invention and Examples do not disclose or enable the formulations of the Challenged Claims, much less such formulations possessing the claimed functionalities. *Id.*; Ex. 1002, Sections VI.C-D. Accordingly, the '231 patent is PGR eligible and the Challenged Claims are not entitled to an effective filing date before March 13, 2013.

Claim 27 recites a broad genus of formulations comprising: (1) 10-50 mg/ml of the claimed VEGF Trap; (b) any amount of any buffer comprising any histidine (free base or salt form, racemate or enantiomerically pure); (3) an organic co-solvent comprising any polysorbate and amount thereof; (4) a stabilizing agent that can be any sugar, any amino acid (or any combination thereof) and any amounts thereof; and (5) a potency limitation. Ex. 1002, ¶94.

Claim 30 depends from claim 27 and further provides that the potency limitation is achieved "after 24 months of storage at 5° C." Ex. 1001, 21:15-17. Claim 47 depends indirectly from claim 27 and further recites that the formulation includes "a tonicity agent." *Id.* at 22:29-30.

As an initial matter, the provisional application does not even mention the percent relative potency of formulations disclosed therein. Ex. 1002, ¶94. The

priority applications also do not provide any potency information for the claimed genera of formulations, or even a single formulation within the scope of claims 27, 30, and 47. *Id.* The only potency information provided in any of the priority applications, including their original claim sets, is in Example 5 of the non-provisional application. Ex. 1002, ¶86; Ex. 1001, 10:56-12:31. However, the formulations tested in Example 5 are outside the scope of claims 27, 30, and 47. Ex. 1002, ¶86. Data for the first formulation are disclosed in Table 8, but that formulation includes 100 mg/ml of VEGF Trap (above the claimed range) and does not include polysorbate. Ex. 1002, ¶86; Ex. 1001, 10:56-11-31. Data for the second formulation are disclosed in Table 9, but that formulation does not include a histidine buffer. Ex. 1002, ¶86; Ex. 1001, 12:1-31. In fact, the specification demonstrates that, for the only formulation comprising a histidine buffer, the percent relative potency was below the claimed value of 75 well before 24 months. Ex. 1002, ¶87; Ex. 1001, 10:56-11:30. Specifically, Table 8 reports that the histidine-buffered formulation produced a percent relative potency of 65 (below the claimed range) after 3 months and 24 hours. *Id.* No relative potency data are provided beyond that time-period. *Id.* Thus, the priority applications fail to provide written description support and fail to enable the subject matter of claims 27, 30, and 47.

The priority applications fail to provide written description support and enable the full scope of claim 47 for the additional reason that they do not disclose a "tonicity agent." In fact, the term is not mentioned in any priority application (including the claims) and was first mentioned in the claims added on June 19, 2020, during prosecution of the '610 application. Ex. 1002, ¶¶163, 200; Ex. 1006, 122-126; *see also* Ex. 1007. The priority applications do not provide support for the genus encompassed by "a tonicity agent" and do not suggest that the inventors were in possession of the claimed formulations comprising any tonicity agent. Ex. 1002, 200. To the extent NaCl is disclosed with its function, it is disclosed as a thermal stabilizer. Ex. 1002, ¶200; Ex. 1001, 2:19-20. Thus, it is clear that the inventors were not in possession of the full scope of claim 47 based on the disclosures in the priority applications.

For at least these reasons, the applications leading to the '231 patent do not provide adequate written description for and do not enable the full scope of the claimed genera of formulations recited in claims 27, 30, and 47, and the '231 patent is PGR eligible.

XI. THE CLAIMS ARE UNPATENTABLE UNDER 37 C.F.R. § 42.204(B)

A. Ground 1: The Challenged Claims are Unpatentable under 35 U.S.C. § 112 for Lack of Written Description

1. Legal Standard for Written Description

"[F]or a claim to a genus, a patentee must disclose 'a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can "visualize or recognize" the members of the genus.'" *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1373 (Fed. Cir. 2017) (quoting *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (*en banc*). Additionally, "one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326-27 (Fed. Cir. 2000). "In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure." *Id.*

2. The Specification Does Not Provide Adequate Written Description for Independent Claims 1, 27, and 31

Independent claims 1, 27, and 31 lack written description support. The '231 patent specification fails to disclose the combination of elements set forth in Claims 1, 27, and 31. Ex. 1002, ¶¶166-167. Rather, it describes several different "aspects," which do not correspond to the claimed formulations. Ex. 1002, ¶¶168-

185; Ex. 1001, 2:4-3:52. Claims 1, 27, and 31 instead recite features selected from isolated disparate embodiments or results in the specification and assembled *post hoc*, contrary to well-established Federal Circuit precedent. *See Nuvo Pharms. (Ir.) Designated Activity Co. v. Dr. Reddy's Labs. Inc.*, 923 F.3d 1368, 1380 (Fed. Cir. 2019), *cert denied*, 140 S. Ct. 902 (2020) ("We have expressly rejected the 'argument that the written description requirement…because the claim language appears in *ipsis verbis* in the specification.'"); *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) ("A description which renders obvious the invention for which an earlier filing date is sought is not sufficient."); *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013) ("Taking each claim—as we must—as an integrated whole rather than as a collection of independent limitations….").

Further, the claims encompass broad, functionally-defined genera of formulations requiring stability, potency, or binding properties. "When a patent claims a genus using functional language to define a desired result, 'the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.'" *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299 (Fed. Cir. 2014) (*quoting Ariad Pharms., Inc.*, 598 F.3d at 1349); *Juno Therapeutics*,

Inc. v. Kite Pharma, Inc., No. 2020-1758, 2021 WL 3778381, at *3 (Fed. Cir. Aug. 26, 2021). "[M]erely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species." *Ariad Pharms Inc.*, 598 F.3d at 1349-50; *see also Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997).

Despite claiming a genus of formulations using functional language to define desired results (*e.g.*, stability, potency, or binding), the specification provides no guidance or common structural features for use in a formulation to obtain the claimed functionalities. Ex. 1002, ¶¶188-192. In fact, the '231 patent discloses no examples falling with the scope of the independent claims, much less a sufficient number of species to demonstrate PO invented the claimed genera of formulations. *Juno Therapeutics, Inc.*, 2021 WL 3778381, at *5 ("But this patent provides nothing to indicate that the inventors possessed the full scope of the genus that they chose to claim."). Thus, the '231 patent lacks adequate written description for the Challenged Claims.

a. The '231 Patent Specification Discloses Different Formulations than Those Claimed, Which Do Not Constitute "Blaze Marks" Directing a POSA to the Claimed Genera of Formulations

The '231 patent does not provide written description support for the claimed genera of formulations. The '231 patent is purportedly directed to ***five*** "aspects" of

the invention, which all differ from the claimed genera of formulations. Ex. 1002, ¶¶168-185. The specification disclosures relating to these five different "aspects" fails to provide the requisite "blaze marks" directing POSAs to the claimed genera. *See Purdue Pharma L.P.*, 230 F.3d at 1326-27. Instead, the Challenged Claims improperly pick and choose various elements from the separate "aspects." *See, e.g.*, *Novozymes A/S*, 723 F.3d at 1349. As the '231 patent fails even to disclose the claimed genera, it clearly fails to disclose structural features common to the genera to enable a POSA to "visualize or recognize" members of the genera. *See Amgen Inc.*, 872 F.3d at 1373 (quoting *Ariad Pharms., Inc.*, 598 F.3d at 1350). In fact, the specification fails to discuss the claimed functional properties in the context of the claimed genera of formulations. *Ariad Pharms., Inc.*, 598 F.3d at 1351.

The ***first aspect*** relates to stable liquid formulations of VEGF Trap comprising a phosphate and/or citrate buffer and a thermal stabilizer comprising NaCl and/or sucrose. Ex. 1002, ¶169; Ex. 1001, 2:4-20. This is distinguishable from the claimed genera of formulation because it, *inter alia*: (1) is limited to liquid formulations; (2) fails to disclose a histidine buffer; (3) fails to disclose "an organic co-solvent comprising a polysorbate;" and (4) fails to disclose any sugar besides sucrose or any amino acid as a stabilizing agent. Ex. 1002, ¶¶170-171; Ex.

1001, 2:4-34. Thus, the first aspect clearly does not provide written description support for independent Claims 1, 27, and 31.

The ***second aspect*** relates to "a high concentration stable liquid formulation of a VEGF antagonist comprising 1-50 mM histidine, 25-150 mM NaCl, 5-30% sucrose, 50-100 mg/ml VEGF Trap, at a pH of about 5-6.5, and either 0.1-0.5% polysorbate or 1-5% PEG." Ex. 1002, ¶173; Ex. 1001, 2:35-49. The second "aspect" is distinguishable from the claimed genera of formulation because it, *inter alia*: (1) is limited to liquid formulations; (2) fails to disclose formulations comprising 10-50 mg/ml VEGF Trap; (3) fails to disclose "an organic co-solvent comprising a polysorbate;" and (4) fails to disclose any sugar besides sucrose or any amino acid as a stabilizing agent. Ex. 1002, ¶¶174-175; Ex. 1001, 2:35-49.

With respect to point (2) above, the disclosed range of VEGF Trap concentrations (*i.e.*, 50-100 mg/ml) overlaps the claimed range (*i.e.*, 10-50 mg/ml) at a single point (*i.e.*, 50 mg/ml). Ex. 1002, ¶173; Ex. 1001, 2:39-49. The Federal Circuit has repeatedly held that such limited disclosure cannot provide support for an entire range. *See Eiselstein v. Frank*, 52 F.3d 1035, 1040 (Fed. Cir. 1995) (disclosure of range of 45 to 55 percent did not provide support for later claims including a range of 50 to 60 percent); *In re Lukach*, 442 F.2d 967, 969-70 (C.C.P.A. 1971); *Gen. Hosp. Corp. v. Sienna Biopharms., Inc.*, 888 F.3d 1368, 1371-73 (Fed. Cir. 2018) ("The disclosure of a broad range of values does not by

itself provide written description support for a particular value within that range."). Similarly, the claimed ranges of all of the excipients disclosed in the second aspect are also significantly more limited than the limitless ranges of the independent claims in the '231 patent, and thus, cannot provide written description support for the claims. *In re Lukach, 442 F.2d at, 969-70.*

With respect to point (3) above, while the second aspect discloses polysorbate as an optional excipient, a POSA would not have understood it to disclose polysorbate as a component of an organic co-solvent. Ex. 1002, ¶175.

The disclosure relating to the second aspect also fails to provide written description support for the claimed genera of formulations exhibiting the claimed stability, potency, and binding limitations. Although directed to formulations different from those claimed in critical ways, claim 1 appears to rely on the second aspect's recited percent degradation value for formulations comprising 75 and 100 mg/ml VEGF Trap. Ex. 1002, ¶176; Ex. 1001, 2:44-49. A POSA, however, would have understood that the disclosure of stability data relating to these formulations would not necessarily mean that PO was in possession of different formulations, comprising different excipients at different concentrations, also possessing the claimed stability. Ex. 1002, ¶176.

Moreover, POSAs would have understood that the "data in Table 7 do not adequately support claims to formulations exhibiting "less than about 3%

degradation." Ex. 1002, ¶177; Ex. 1001, 10:42-54. Example 4 contains several exemplary high concentration formulations comprising 50, 75, and 100 mg/ml of VEGF Trap that relate to the second aspect. Ex. 1002, ¶¶177-178; Ex. 1001, 10:27-55. Table 7 reports the results of SE-HPLC, which it labels "% Degradation." Ex. 1001, Table 7. However, SE-HPLC only measures a subset of the % degradation in a formulation, and fails to measure contributions from other degradation pathways. Ex. 1002, ¶177. Thus, the reported data do not properly support that the formulations in the second "aspect" have less than 3% degradation after the reported storage times. *Id*. The second aspect is also completely silent on the potency and binding limitations of claims 27 and 31.

The ***third aspect*** discloses "a pre-lyophilized formulation" comprising "5-50 mM histidine, 0.1-3.0% PEG, 0.25-3.0% glycine, 0.5-6.0% sucrose, and 5-75 mg/ml of the fusion protein, at a pH of about 6.0-6.5." Ex. 1002, ¶179; Ex. 1001, 2:63-66. It is distinguishable from the claimed genera of formulations because it, *inter alia*: (1) is limited to pre-lyophilized formulations; (2) fails to disclose formulations comprising 10-50 mg/ml VEGF Trap; (3) fails to disclose "an organic co-solvent comprising a polysorbate;" and (4) fails to disclose any sugar besides sucrose or any amino acid besides glycine as a stabilizing agent. Ex. 1002, ¶180; Ex. 1001, 2:63-3:34.

With respect to point (2) above, like the second aspect, the third aspect of the invention discloses a different range of fusion protein. In particular, it discloses ranges of fusion proteins of "5-75 mg/ml" and "12.5 to 75 mg/ml." Ex. 1002, ¶181; Ex. 1001, 2:63, 3:8. A POSA would have understood that the inventors were not in possession of the claimed sub-genus of "10-50 mg/ml" by the disclosure of these broader genera. *See, e.g., In re Lukach*, 442 F.2d at 969-70; *Purdue Pharma L.P.*, 230 F.3d at 1328 ("There is therefore no force to Purdue's argument that the written description requirement was satisfied because the disclosure revealed a broad invention from which the [later-filed] claims carved out a patentable portion."). Additionally, the claimed ranges of the other disclosed excipients are also significantly more limited than the limitless ranges of the independent claims in the '231 patent, and thus, cannot provide written description support for the claims. *See, e.g.*, *Eiselstein*, 52 F.3d at 1040; *In re Lukach*, 442 F.2d at 969-70.

With respect to point (3) above, while the third aspect discloses polysorbate as an optional excipient, (Ex. 1002, ¶181; Ex. 1001, 2:63-3:2), the third aspect only discloses PEG as an organic co-solvent. Ex. 1001, 2:59 ("the organic co-solvent or bulking agent is PEG"). Ex. 1002, ¶181. A POSA would not have understood the inventors to be in possession of formulations comprising an organic co-solvent comprising polysorbate. *Id.*

In addition to the above differences, the disclosure relating to the third aspect fails to provide any written description support for the formulations exhibiting the claimed stability, potency, and binding limitations. *See Nuvo Pharms.*, 923 F.3d at 1382. With respect to the stability limitation, the '231 patent does not provide any data regarding this limitation. Ex. 1002, ¶¶182-183; Ex. 1001, 10:15-27, 10:59-11:30. Example 4 includes a formulation related to the third aspect, but rather than provide the data as it did for other disclosed formulations, the specification merely reports that "stability studied [sic] showed no degradation of the VEGF trap was detected after 6 months of storage at 2-8ºC." Ex. 1002, ¶183; Ex. 1001, 10:15-27. The specification does not report the degradation after the much longer time period of 15 months or at 5º C as required by claim 1, and thus POSAs would not have understood that PO possessed a formulation (much less the entire genus) meeting this limitation. Ex. 1002, ¶183.

With respect to the potency and binding limitations, Example 5 includes a formulation related to the third aspect, but the values reported in Table 8 fall below those claimed in claims 27 and 30, respectively. Ex. 1002, ¶184; Ex. 1001, 10:55-11:32. Thus, a POSA would not have understood from this data that the inventors were in possession of the claimed formulations.

The ***fourth*** and ***fifth aspects*** disclose methods of producing a lyophilized formulation of a VEGF Trap, and a method of producing a reconstituted

lyophilized formulation of a VEGF Trap. Ex. 1002, ¶185; Ex. 1001, 3:35-4:4. These aspects are unrelated to the Challenged Claims. Ex. 1002, ¶185.

As set forth above and illustrated in the table on pages 8-9, the claims overreach the scope of the disclosure in the specification. *See Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000); *LizardTech Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005). None of the disclosed genera of formulations corresponds to the claimed genera of formulations. Ex. 1002, ¶186. Further, the specification is completely lacking with respect to several claim limitations. *Id.* ¶187. For example, the ***only*** specific organic co-solvent disclosed is PEG. Ex. 1002, ¶¶189-190; Ex. 1001, 5:17-21 ("In the formulations of the invention, PEG 3350 is an organic co-solvent which is used to stabilize the fusion protein…"). The specification fails to disclose an organic co-solvent comprising polysorbate. Ex. 1002, ¶¶189-190. Further, the specification only discloses one of each species of a thermal stabilizer (*i.e.*, glycine and sucrose) that is within the claimed genera of thermal stabilizers (*i.e.*, any amino acid and any sugar).[8] Ex. 1002, ¶191; Ex. 1001, 6:58-61. Moreover, the specification would not

[8] While the specification discloses other sugars as "bulking agents," there is no disclosure in the '231 patent that would have suggested these other sugars are thermal stabilizers and interchangeable as such with sucrose. Ex. 1002, ¶206; Ex.

have demonstrated to a POSA that PO was in possession of the entire claimed genera exhibiting the claimed stability, potency, and binding properties. Ex. 1002, ¶¶188-189, 192. Thus, the specification does not support the entire breadth of claimed genera of formulations.

b. The '231 Patent Does Not Disclose a Representative Number of Species Relative to the Claimed Genera of Formulations

The '231 patent fails to disclose a single example within the scope of the claims, much less sufficient representative species to establish possession of the broad genera of functionally-claimed formulations. *Ariad Pharms., Inc*, 598 F.3d at 1349. The '231 patent only discloses a single exemplary formulation comprising both histidine and polysorbate as required by all of the '231 patent claims. Ex. 1002, ¶¶189, 197; Ex. 1001, 10:27-41. However, POSAs would not have considered polysorbate or any of the formulation's excipients to be an organic co-solvent as required by the claims. Ex. 1002, ¶¶189, 215.

However, even if this single formulation were considered to include the claimed excipients, it is outside the scope of the claimed "wherein" clauses. With

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1001, 5:7-21. Further, the specification fails to disclose formulations containing any amino acid except glycine. Ex. 1002, ¶191; Ex. 1001, 6:58-61.

respect to claim 1's stability limitation, the specification only evaluated the formulation using SE-HPLC (measuring only a subset of total degradation) after 24 months of storage. Ex. 1002, ¶¶177, 263; Ex. 1001, 10:38-55. The '231 patent does not provide data for all forms of degradation. Ex. 1002, ¶177; Ex. 1001, 10:42-54 (Table 7, row 2). Further, no disclosure in the specification supports the full range of degradation percentage in the claims (*i.e.*, from 0% to 3%). Thus, a POSA would not have recognized that the alleged inventors were in possession of the broadly claimed formulations having the claimed stability properties. *See, e.g.*, *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1123-28 (2008) (holding that patentee failed to satisfy written description requirement and disclosure of a single species could not support a broadly claimed genus); *Regents of the Univ. of Cal.*, 119 F.3d at 1569.

With respect to claims 27 and 31 and their dependent claims, the specification does not provide ***any*** potency or binding data for ***any*** formulation comprising histidine and polysorbate. Ex. 1002, ¶¶188-189. In fact, Example 5 is the only example containing any potency or binding data in the entire specification. Ex. 1002, ¶¶86, 184; Ex. 1001, 10:56-12:31. However, neither example in Example 5 comprises polysorbate, and the second embodiment also lacks a histidine buffer. Ex. 1002, ¶¶84, 86; Ex. 1001, 10:56-12:31. In addition to these deficiencies, the data show that the first formulation (histidine, no polysorbate)

exhibited a percent relative potency of 65 (below the claimed range) after just 3 months and 24 hours. Ex. 1002, ¶87; Ex., 1001, 11:17-31, Table 8. With respect to the binding limitation of claim 31, the data suggest that the first formulation (histidine, no polysorbate) exhibited a percent relative binding of less than 88 after 1 month, 1 month + 4 hours, and 1 month + 24 hours, which oddly increased to 98 after 3 months. Ex. 1002, ¶87; Ex. 1001, 10:56-11:31, Table 8.

Thus, in view of these differences in formulation excipients and data deficiencies (and in fact, data contradicting possession in some instances), POSAs would not have recognized PO was in possession of the claimed formulations, much less those possessing the claimed functionalities.

3. The Specification Does Not Provide Adequate Written Description for the Dependent Challenged Claims

The dependent Challenged Claims suffer from the same deficiencies as the independent claims, and merely provide a broad range of a certain excipient (*e.g.*, 5-50 mM histidine or 10 mM histidine) or provide a single species of excipient within the claimed genus (*e.g.*, polysorbate 20 as the polysorbate) does not remedy the specification's failure to disclose the claimed combination of features or sufficient representative species. Ex. 1002, ¶¶193-209.

Moreover, several of the dependent claims introduce additional written description defects. For example, claims 5, 17, 46, and 60 recite that the formulation comprises 40 mg/ml VEGF Trap. However, the specification does not

disclose a single histidine-buffered formulation comprising 40 mg/ml VEGF Trap, much less in combination with the other claim elements. Ex. 1002, ¶199. Any attempt by the PO to rely on a range (much less one for a formulation outside the claims) would also fail, as the disclosure of a large range does not provide support for this claim. *See, e.g.*, *Gen. Hosp. Corp.*, 888 F.3d at 1371-73 ("The disclosure of a broad range of values does not by itself provide written description support for a particular value within that range.").

As another example, claims 6, 18, 47, and 61 provide that the formulation further comprises a "tonicity agent" which is only recited in the claims and is not disclosed in the specification. Ex. 1002, ¶¶163, 200. While the specification discloses NaCl, it is disclosed as a thermal stabilizer—not a tonicity agent. Ex. 1002, ¶200; Ex. 1001, 2:19-20. The specification fails to demonstrate to a POSA that the inventors were in possession of formulations containing the undefined genus of "tonicity agents," much less formulations comprising any amount of any tonicity agent. Ex. 1002, ¶200.

As yet another example, claims 11, 21, 53, and 67 recite that the sugar is selected from the "group consisting of dextrose, ribose, fructose, mannitol, inositol, sorbitol, trehalose, sucrose, and lactose." None of these claims is supported by the specification, which only discloses sugars other than sucrose as "bulking agents."

Ex. 1002, ¶¶206-207; Ex. 1001, 5:8-21. A POSA would not have understood that all bulking agents would function as a stabilizing agent.

Thus, the dependent Challenged Claims, including claims 2-11, 17-21, 28-30, 32, 41-53, and 58-67 are invalid for lack of written description.

B. Ground 2: The Challenged Claims are Unpatentable under 35 U.S.C. § 112 for Lack of Enablement

1. Legal Standard for Enablement

The specification must enable a POSA to make and use the claimed invention. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). Further, the disclosure of the specification must be commensurate in scope with the claim under consideration. *See In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991); *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993).

A disclosure which calls for undue experimentation is not enabling. The "*Wands* factors" may be considered when determining whether a disclosure calls for undue experimentation, including: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

2. The Specification Does Not Enable Independent Claims 1, 27, and 31

First, with respect to factor (4), the nature of the invention relates to broad genera of formulations claimed by their function. Ex. 1002, ¶218; ; Ex. 1001, 19:35-45, 20:64-21:9, 21:18-29. "While functional claim limitations are not necessarily precluded in claims that meet the enablement requirement, such limitations pose high hurdles in fulfilling the enablement requirement for claims with broad functional language." *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1087 (Fed. Cir. 2021). Far short of meeting this "high hurdle," the specification provides essentially no disclosure specific the claimed genera of formulations, and the data contradict the functionality required by the claims (*e.g.*, Table 8 potency data are below the claimed 75 percent relative potency). Ex. 1002, ¶¶ 184, 218; *see also* Section XI.A. Such limited and contradictory disclosures would not have enabled a POSA to make and use the full scope of claimed formulations without undue experimentation. *Id.* ¶218.

Second, with respect to factor (7), the alleged invention is directed to what PO has admitted is an unpredictable art—biological formulations. *Id.* ¶219; Ex. 1046, ¶10. PO has argued that development of protein formulations is unpredictable and slight changes in excipients and concentrations thereof can impact the overall profile of a formulation. Ex. 1002, ¶220; Ex. 1047, ¶¶5-10. Further, the Federal Circuit has repeatedly recognized the same. *See Amgen Inc.*,

987 F.3d at 1087-88; *Purdue Pharma L.P. v. Depomed, Inc.*, 643 F. App'x 960, 964 (Fed. Cir. 2016); *HZNP Medicines LLC v. Actavis Labs. UT, Inc.*, 940 F.3d 680, 703 (Fed. Cir. 2019), *cert. denied sub nom.*, 141 S. Ct. 662 (2020).

Third, with respect to factor (8), the scope of the claims is broad with the primary limitations being the "wherein" clauses rather than the formulation components. Ex. 1002, ¶¶211-217. The claimed "formulations" include liquid or lyophilized formulations that "can be reconstituted into solutions, suspensions, emulsions or any other suitable form for administration or use." Ex. 1002, ¶212; Ex. 1001, 6:10-11. Further, the claims encompass a formulation suitable for any route of administration. Ex. 1002, ¶212. The broad claims also encompass formulations comprising numerous permutations of excipients, most of which can be present in any concentration. *Id.* ¶¶214-16. The independent claims encompass an incalculably large number of formulations, and Petitioner's expert, Dr. Tarantino, has provided a very conservative calculation that the claimed excipients encompass over 4,800,000 formulations to be tested. *Id.* ¶¶77, 211. The '231 patent's limited disclosure fails to enable the full scope of these formulation permutations and highly variable concentrations. *See, e.g.*, *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1384 (Fed. Cir. 2012) ("MagSil did not fully enable its broad claim scope.").

Fourth, with respect to factor (2), the '231 patent provides minimal, if any, guidance on how to obtain the claimed formulations having the stability, potency, or binding properties. Ex. 1002, ¶¶221-230. As detailed in Section XI.A, above, the specification discloses five different "aspects," none of which corresponds to the claimed genera of formulations. *Id.* ¶¶79-83, 221-230. Further, the '231 patent provides no guidance regarding structural commonalities that can be incorporated into a formulation to produce formulations having the claimed stability, potency, and binding properties. *Id.* ¶¶221-222. Instead, the only discussions of these limitations are in the context of formulations outside of those claimed. *Id.* ¶¶230-234; Ex. 1001, 10:55-12:31. Moreover, as discussed in Section XI.C with respect to indefiniteness, the specification fails to even adequately explain to a POSA the appropriate methodology to determine whether a formulation exhibits the claimed stability, potency, or binding property, let alone how to make formulations with the claimed functionalities. Ex. 1002, ¶¶261-281. Thus, the specification fails to demonstrate with reasonable specificity how to make and use a reasonable number of potential embodiments across the full scope of the claims. *See Pharm. Res., Inc. v. Roxane Labs., Inc.*, No. 03-3357, 2006 WL 3231427 (D.N.J. Nov. 8, 2006), *aff'd*, 253 F. App'x 26 (Fed. Cir. 2007) (holding broad claims reciting the presence of "a surfactant" that covered any and all surfactants were not enabled).

Fifth, with respect to factor (3), the specification fails to disclose any working examples for the claimed formulations. Ex. 1002, ¶¶231-234. Only one example in the specification includes both histidine and polysorbate. *Id.* ¶232; Ex. 1001, 10:27-31 (disclosing a liquid formulation comprising "10 mM histidine, 50 mM NaCl, 5-20% sucrose, 50-100 mg/ml VEGF trap, and one of 0.1% polysorbate 20 or TY° PEG 3350."). The example, however, fails to disclose "an organic co-solvent comprising polysorbate," because POSAs would have understood that none of the excipients in the example were an organic co-solvent. Ex. 1002, ¶¶232.

In addition to only disclosing formulations outside the claims, the '231 patent's working examples do not indicate that the claimed formulations would exhibit the stability, potency, or binding properties set forth in claims 1, 27, and 31, respectively. *Id*. ¶233. As discussed in Section XI.A., the "% Degradation" reported in Table 7 merely represents "[t]he amount of degradation determined by SE-HPLC." Ex. 1002, ¶233; Ex. 1001, 10:38-55. A POSA would have understood that SE-HPLC measures only a portion of protein degradation and fails to measure other degradation forms, including those disclosed in the '231 patent. Ex. 1002, ¶233; *see* Ex. 1001, 4:35-54. No other degradation values are reported, much less for the claimed formulations.

Regarding potency and binding, Example 5 provides the only data for histidine-buffered formulations, but Example 5 is outside the scope of the claims,

because the formulations lack polysorbate. Ex. 1002, ¶234. Moreover, the specification's bioassay and binding assay results fall below the claimed values, indicating that claimed functionalities were not achieved. *See* Ex. 1002, ¶184, 234; Ex. 1001 at Table 8 (reporting a percent relative potency of 65 (below the claimed 75 value) and a percent relative binding of 74, 72, and 81 (below the claimed 88 minimum, albeit at time periods prior to the claimed 3-month time period)). Because the specification evidences that those formulations do not possess the claimed functionalities, the specification does not enable POSAs to make other formulations (falling within the scope of the claims) that possess the claimed functionalities.

Sixth, with respect to factor (1), the quantity of experimentation necessary for a POSA to practice the full breadth of formulations is undue. Ex. 1002, ¶235. In particular, the amount of experimentation necessary to make the more than 4,800,000 formulations encompassed by the claims is undue. Moreover, the additional experimentation necessary to assess whether they have any of the claimed functional properties is undue. Ex. 1002, ¶¶77, 235.

Formulations: The claims encompass any type of formulation and for any administration route. However, the '231 patent fails to provide a single example of a formulation within the scope of the claims, much less across the full claim scope (*e.g.*, a lyophilized, solid, or intravitreal formulation). Ex. 1002, ¶236. In addition,

the specification contemplates formulations, such as lyophilized formulations that are reconstituted as emulsions, which are uncommon and difficult to produce. Ex. 1002, ¶236; Ex. 1001, 6:10-11. The breadth of claimed formulations would have required undue experimentation and development to create, and identifying combinations of the claimed excipients possessing the claimed stability, potency, and binding properties would have required undue experimentation. *Id.* ¶238. Further, the specification provides only passing reference to two types of administration—subcutaneous and intravenous. Ex. 1002, ¶236; Ex. 1001, 10:8-10. There is no discussion of any other type of administration, *e.g.*, intravitreal, or how to render formulations suitable for such administration. Ex. 1002, ¶226.

VEGF Trap: The claims require 10-50 mg/ml VEGF Trap, yet the specification only discloses histidine-buffered examples with concentrations of fusion protein either at or above the claimed range's upper limit (*i.e.*, 50, 75, or 100 mg/ml VEGF Trap). Ex. 1002, ¶84; Ex. 1001, 10:4-55, Example 4. A POSA would have understood that the fusion protein itself can act as a buffer at higher concentrations. Ex. 1002, ¶227; Ex. 1048, 3:15-21. Thus, reducing the VEGF Trap's concentration as claimed would have been understood to reduce the overall buffering capacity of the formulation. *Id.* Yet, the '231 patent does not provide any guidance on formulating lower concentration VEGF Trap formulations that are sufficiently buffered. Ex. 1002, ¶227. Thus, in view of the limited guidance,

undue experimentation would have been required to formulate and identify lower concentration VEGF Trap formulations having the claimed functionalities, especially with low concentration histidine buffer.

Organic co-solvent comprising polysorbate: A POSA would not have understood the specification to disclose formulations comprising an organic co-solvent comprising polysorbate. Ex. 1002, ¶237. Further, it would have been extremely difficult, requiring excessive experimentation, to create lyophilized formulations comprising an organic co-solvent comprising a polysorbate given that polysorbates, such as Tween 20, are typically oils at room temperature. *Id.*, ¶224-25. The '231 patent is silent on how to do so. *Id.*

Stabilizer: The claims encompass any stabilizer comprising a sugar, an amino acid, or combinations thereof, and it would have required excessive experimentation to produce formulations having functionalities over the full breadth of these genera. Ex. 1002, ¶¶216, 229; Ex. 1045, 5191, table II, table III. A POSA would have understood there to be numerous different sugars and amino acids encompassed by the claims. *Id.* Yet, the '231 patent only provides a single example of each (*i.e.*, sucrose and glycine) and no guidance on how to create a workable formulation with any of the other species within these genera. Ex. 1002 ¶ 229.

Seventh, with respect to factor (5), while there were numerous disclosures of the claimed VEGF Trap (*see* Section XI.D., below), the overall state of the art fails to remedy the deficiencies of the specification. Ex. 1002, ¶¶240-241.

Eighth, with respect to factor (6), the relative skill of the art was someone with an advanced degree and two years of protein or peptide formulation work. Even with this relative skill, a POSA would not have been able to produce the full scope of the claimed invention in view of the enormous amount of experimentation required and lack of guidance provided by the '231 patent. Ex. 1002, ¶239. PO has expressly represented that a POSA, even with the knowledge of a common excipient handbook such as Remington's Pharmaceutical Sciences 16th edition, would "expect to engage in significant non-routine experimentation to develop a successful formulation" and that "the parameters used to select the ingredients are empirical and cannot be predicted." Ex. 1002, 239; Ex. 1050 at 17 (12/06/16 OA Response in Appl. No. 15/150,840).

Despite this alleged lack of guidance in the prior art, the '231 patent provides very little guidance and insufficient representative species supporting the expansive claim scope and desired functionalities. Ex. 1002, ¶221-230. Thus, the '231 patent fails to provide sufficient guidance to overcome—by PO's own admission—the unpredictability in developing stable VEGF Trap formulations. A POSA would thus need to engage in undue experimentation to arrive at the full

scope of claimed formulations. *Id.* ¶227. As a result, independent claims 1, 27, and 31 are invalid due to lack of enablement.

3. The Specification Does Not Enable the Dependent Challenged Claims

The dependent Challenged Claims are also not enabled for the same reasons discussed in detail for the independent claims. They do not substantially narrow the scope of the claims, and the specification fails to provide sufficient guidance for the genera of formulations claimed therein.

Some, such as claims 29 and 30, are directed to the same breadth of formulations but add limitations regarding the time period at which the claimed potency should be determined. Ex. 1002, ¶¶259-260. No potency data are disclosed for formulations falling within the scope of these claimed formulations. *Id.* Moreover, with respect to claim 30's 24-month potency limitation, no data are provided for anywhere near this claimed time period for a histidine-buffered formulation as the provided data ends at 3 months + 24 hours. Ex. 1002, ¶260; Ex. 1001, 10:55-11:30. Thus, the '231 patent does not teach POSAs how to make and use even a single formulation, much less working formulations for the entire range, possessing the claimed potency. Ex. 1002, ¶¶259-260.

Other claims provide only a broad range or concentrations, or sometimes a concentration, for only a single excipient (histidine in claims 2, 3, 28, 32, 43, 44, 58; Ex. 1002, ¶¶242-244), or a subset of excipients (claims 41, 50, 64; Ex. 1002,

¶¶255-256), but are otherwise as broad as the independent claim formulations. Solely providing a range or concentration for one claimed excipient, or some but not all excipients, does not teach POSAs how to make the claimed genera of formulations possessing the claimed properties, particularly given the lack of working examples across the range claimed. Ex. 1002, ¶¶242-244, 255-256.

Other claims are similar but do not even limit at least one excipient for which a range is provided to a single species (the polysorbate ranges of claims 8, 42, 49, 51, 63, 65), and are likewise not enabled. *Id.* ¶254.

Like these claims, claims 4, 45, and 59 depend from independent claims or claims adding only a 5-50 mM histidine limitation, but add a pH range of 6.0-6.5. Ex. 1001. They are and are otherwise directed to broad genera of formulations and excipients—and the ’231 patent fails to report pH for the only histidine-buffered formulation containing polysorbate (Example 4)—thus these claims also are not enabled by the ’231 patent’s disclosures. Ex. 1002, ¶¶245-247.

In other claims, for at least one of the excipients, the claims will recite a limitation to a subset of the genus (*e.g.*, claims 10-11, 20-21, 52-53, 66-67, reciting that the stabilizer is a sugar or a list of sugars and alcohol sugars) or recite a species (*e.g.*, claim 9, reciting polysorbate 20), but concentration ranges are not recited. Ex. 1002, ¶¶257-258; Ex. 1001. Moreover, the specification only teaches using a single species of sugar (sucrose) as the sugar in a VEGF Trap formulation.

Ex. 1002, ¶257. As with the other dependent Challenged Claims, the specification does not teach POSAs how to make and use the entire range of formulations encompassing all genera of the various excipients across the full breadth of possible concentrations, much less formulations possessing the claimed functional properties. *Id.* ¶¶257, 258. Finally, many of the claims introduce new matter that is not disclosed anywhere in the specification. This includes the 40 mg/ml VEGF Trap in the histidine-buffered formulations of claims 5, 17, 46, and 60 as well as the tonicity agent of claims 6-7, 18-19, 47-48, and 61-62. Ex. 1002, ¶¶248-253. Given the lack of disclosure for—much less guidance for how to make and use—formulations containing these claim elements, undue experimentation would be required and the claims are not enabled. *Id.*

For at least these reasons, and as explained in detail in the Tarantino Declaration (Ex. 1002, ¶¶242-260), the dependent Challenged Claims are not enabled.

C. Ground 3: The Challenged Claims are Unpatentable under 35 U.S.C. § 112 for Indefiniteness

1. Legal Standard for Indefiniteness

Under § 112, second paragraph, "a patent is invalid for indefiniteness if its claims, read in light of the specification . . . and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the

invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014). The Board applies the *Nautilus* standard in AIA post-grant proceedings.

A claim is indefinite "when (1) different known methods exist for calculating a claimed parameter, (2) nothing in the record suggests using one method in particular, and (3) application of the different methods result in materially different outcomes for the claim's scope such that a product or method may infringe the claim under one method but not infringe when employing another method." *Ball Metal Beverage Container Corp. v. Crown Packaging Tech., Inc.*, 838 F. App'x. 538, 542 (Fed. Cir. 2020) (citations omitted).

For example, in *Teva*, the Federal Circuit affirmed an indefiniteness finding because there were at least three ways to measure and report "molecular weight," each method would produce different results, the patent did not give guidance as to which specific method to use, and the prosecution history contained two contradictory statements regarding which measuring method to use. *See Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341-45 (Fed. Cir. 2015); *see also Dow Chem. Co. v. Nova Chems. Corp.*, 803 F.3d 620, 630-35 (Fed. Cir. 2015).

2. The Stability Limitation Renders Claims 1-11, 17-21, and 41-42 Indefinite

Claim 1 recites "wherein said VEGF antagonist fusion protein exhibits less than about 3% degradation after 15 months of storage at 5º C." This claim term is

indefinite because the "degradation percentage" can be calculated using a number of different methods, the '231 patent recognizes that a number of methods are applicable yet provides no clarity, and the different methods produce different results. Ex. 1002, ¶¶261-262; Ex. 1001, 4:37-44. A POSA would have understood that the specification provides conflicting guidance on how to measure the percent degradation, and the methods would provide different results. Ex. 1002, ¶262; Ex. 1001, 4:37-44. The '231 patent expressly recognizes that there are many degradation pathways for proteins, which exhibit instability in different ways (Ex. 1001, 4:40-44); yet certain of its disclosures contradictorily suggest that "percent degradation" refers to a subset of degradation—degradation detected by SE-HPLC. Ex. 1002, ¶263; Ex. 1001, 10:38-55, Example 4.

Specifically, the '231 patent discloses that "a variety of degradation pathways exist for proteins, implicating both chemical and physical stability. Chemical instability includes deamination, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Physical instability encompasses many phenomena, including, for example, aggregation." Ex. 1002, ¶262; Ex. 1001, 4:38-44. That is, the '231 patent recognizes that there are many forms of protein degradation. *Id.* Based on this disclosure, a POSA would have understood that the recited percent degradation would account for all forms of protein degradation, including, *e.g.*, degradation evidenced by modification to the protein's

secondary or tertiary structure. Ex. 1002, ¶262. These forms of degradation are measured using techniques such as circular dichroism (CD) spectroscopy and intrinsic tryptophan fluorescence spectroscopy (IT-FS). *See*, *e.g.*, Ex. 1002, ¶144; Ex. 1024, 3-4.

In the examples, however, the specification equates percent degradation with ***only a subset*** of degradation measured by SE-HPLC. Ex. 1002, ¶263; Ex. 1001, 10:38-55. Table 7 purports to report "% Degradation" based on those SE-HPLC results alone. *Id.* A POSA, however, would have understood that SE-HPLC merely measures certain types of degradation products and does not account for many other forms of degradation listed in the '231 patent. Ex. 1002, ¶263; Ex. 1001, 4:40-44. The SE-HPLC results would reflect just a subset of the total percent degradation, and thus would produce a significantly different percentage than a comprehensive measurement of "degradation." Ex. 1002, ¶263.

The present case is thus analogous to *Teva*, where the claims-at-issue were held invalid because the intrinsic record provided conflicting and contradictory information on how the claimed molecular weight should be determined, and both methodologies would produce different results. *Teva Pharms. USA, Inc.*, 789 F.3d at 1345. Here, the '231 patent's conflicting guidance on how to determine the percent degradation and the different results that would be obtained by using

different methodologies renders claim 1 and its dependent Challenged Claims indefinite. Ex. 1002, ¶263.

3. The Potency Limitations Render Claims 27-30, and 43-53 Indefinite

Claims 27's potency limitation ("wherein said VEGF antagonist fusion protein is capable of inhibiting biological activity of human VEGF as measured by a mouse Baf/3 VEGFR1/EpoR cell line and achieving a percent a percent relative potency of at least 75 relative to a reference IC_{50} standard") is indefinite because the specification and claims acknowledge that multiple methods can be used to measure the percent relative potency, the '231 patent provides conflicting guidance on what method to use, and the specification confirms that different methods produce different results.

First, claim 27 fails to indicate when the percent relative potency should be measured. Ex. 1002, ¶¶264-266; Ex. 1001, 21:5-9. In fact, the claims encompass multiple different time periods and conditions. *Id.* The data provided in the specification reflect that when the measurement is taken has an enormous effect on the percent relative potency. Ex. 1002, ¶266. For example, Table 8 shows that for one exemplary formulation, the percent relative potency was 117 after one month and 65 after 3 months and 24 hours. *Id.* Thus, the same formulation would be both inside and outside the claimed range depending on when the test was conducted. *Id.*

Second, claim 27 and its dependents are indefinite for the additional reason that a POSA would have known that bioassay results have significant variability depending on how they are created and their methods of measurement. Ex. 1002, ¶267; Ex. 1051, Abstract. Bioassays are difficult to perform and time consuming, which contributes to heightened variability. *See id.* A POSA would have recognized that a cell based assay as required by claim 27, exhibits significant variability and would not have been able to discern with reasonable certainty whether a VEGF-specific fusion protein formulation was within the scope of claim 27. *Id.*

Significant differences in bioassay design methodologies also render the claims indefinite. Ex. 1002, ¶268; Ex. 1051, Abstract. POSAs would have understood that in order for a bioassay to have meaningful results, statistical analysis of the results must be conducted to understand both the sample variability and the performance and reliability of the assay itself. Ex. 1002, ¶268; Ex. 1051 ¶84-85. Such characterization is impossible without the use of a well-understood standard of known potency and stability. Ex. 1002, ¶268; Ex. 1051, 83. Without a detailed understanding of the standard, the assay performance, and the range of expected error, a POSA would have no way of understanding whether the results of the bioassay relate to the sample being tested, the standard that is used, or the

bioassay design and performance, thus rendering the results useless. Ex. 1002, ¶268.

For the above reasons, bioassay analyses are primarily used for preclinical purposes to determine if there is any activity in a given protein in order to select proteins for further development, where precise measurement is unnecessary. Ex. 1002, ¶269; Ex. 1051, 85. They are not ordinarily used by POSAs to quantify a protein's biological activity in a given formulation with specificity, much less to define the metes and bounds of a genus of formulations, precisely because the results are notoriously unreliable. *Id.*

Further, the design strategy is critical for bioassay analysis because they are almost always unique for each given therapeutic, and there are many potential strategies to try to reduce (but not eliminate) the prevalence of error. Ex. 1002, ¶¶270-272; Ex. 1052, 126, 127. Claim 27 is thus indefinite for the additional reason that different bioassay methods yield different results, which in turn, may or may not result in a formulation being within the scope of the claims. Ex. 1002, ¶¶270-272.

Further, the recited "VEGF IC_{50} standard" is not described (including, *e.g.*, its source, its amino acid sequence, its vehicle, its storage condition, or any other information necessary for a POSA to have understood what it is and how to obtain or produce it). Ex. 1002, ¶274, Ex. 1001, 11:4-6. To the extent different bioassays

use different reference standards, the results may differ. Ex. 1002, ¶274. Moreover, even the same reference standard, developed by the same company, is subject to variability from lot to lot due to the nature of biologics, which provides another reason that claim 27 is indefinite. *Id.*

The '231 patent demonstrates that the bioassay used to obtain the disclosed data is unreliable. The results disclosed in Tables 8 and 9 are highly variable such that even using the same type of bioassay (which is presumed, but not expressly disclosed) may result in a formulation being within the scope of the claims one day and outside the scope of the claims the next day. Ex. 1002, ¶276; Ex. 1001, 10:55-12:31, Tables 8-9. For example, Table 8 reports the bioassay result after ***3 months*** is 101, but this drops significantly to 65 after just one day (***3 months* + 24** hours) of storage. Ex. 1002, ¶276; Ex. 1001, Table 8. The cause of such extreme variability is attributable to either a difference in stability based on the time of storage or the well-known variability and prevalence of error in bioassay testing. *Id.* Given the change in results over the course of 24 hours, a POSA would have understood the result differences to be attributable to the latter. Ex. 1002, ¶276.

For these reasons, the wherein clauses render independent claim 27 and its dependent Challenged Claims indefinite. The dependent claims specify testing at 1 or 24 months, but are similarly indefinite due to lack of guidance regarding the methodology and the unreliability of bioassay testing. *Id.*

4. The Binding Limitation Renders Claims 31-32 and 58-67 Indefinite

Claim 31's binding limitation ("wherein said VEGF antagonist fusion protein is capable of binding VEGF at a percent relative binding of at least 88 relative to a reference VEGF IC50 standard, after storage at 5° C. for 3 months") renders it and its dependents indefinite for the same reason described above with respect to claim 27. In particular, a POSA would have known that binding affinity results are notoriously unreliable, and can vary significantly in how they are created and their methods of measurement. Ex. 1002, ¶¶278-280.

The '231 patent confirms this. The binding assay results for Example 5's histidine-buffered formulation are also provided in Table 8. These results vary significantly, for example, going from 126 after 0 months of storage, down to 74 after ***1 month***, up to 81 after ***1 month* +4** hours, and back down to 72 after ***1 month* +24** hours. Ex. 1002, ¶280; Ex. 1001, Table 8.

Furthermore, the '231 patent provides very few details regarding the methodology used to measure the binding property, including the VEGF IC_{50} standard for this assay is also not disclosed. Ex. 1002, ¶¶280-281; *see e.g.*, Ex. 1001, 11:6-12. Thus, these claims are indefinite for the same reason discussed above regarding claim 27. Consequently, claim 31 and its dependent Challenged Claims are indefinite. Ex. 1002, ¶281.

D. Ground 4: The Challenged Claims are Obvious Over Wulff or Fraser in View of Andya

1. Legal Standard for Obviousness

A claim is unpatentable if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966). .

2. Wulff, Fraser, and Andya Are Prior Art

To the extent that the PO argues that the '231 patent satisfies the written description and enablement requirements and the claims are broad enough to encompass formulations disclosed in the '231 patent (e.g., those merely comprising polysorbate without an organic co-solvent), then the prior art discloses formulations within the scope of the claims and the claims are obvious. Specifically, claims 1-4, 6-11, 18-21, 27-32, 41-45, 58-59 of the '231 patent are rendered obvious by Wulff (Ex. 1004) or Fraser (Ex. 1003) in view of U.S.

2001/0014326 ("Andya") (Ex. 1005) under pre-AIA 35 U.S.C. § 103 and post-AIA 35 U.S.C. § 103. Ex. 1002, ¶360.

Wulff, a Regeneron publication, is titled "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2." Ex. 1004, 2797; Ex. 1002, ¶283. Wulff is prior art based on its publication (July 2002[9]) more than one year prior to the '231 patent's earliest possible priority date of March 22, 2006. Ex. 1002, ¶283. Thus, Wulff qualifies as prior art under pre-AIA 35 U.S.C. 102(b) and post-AIA 35 U.S.C. 102(a)(1). *Id.* PO failed to disclose this reference to the Examiner and the Examiner erred by not finding it and by not issuing any prior art rejections despite the copious prior art disclosures of the claimed VEGF TrapR1R2 protein and formulation and advantageous histidine buffer systems.

Fraser was published in the Journal of Clinical Endocrinology & Metabolism in February 2005 and indicates that it was first published online on November 23, 2004. Ex. 1003, 1114. Rachel Watters, the Head of Resource Sharing for UW-Madison's General Library System confirms that Fraser was received by the Library on or before February 15, 2005, and was indexed and

[9] PO admitted Wulff's July 2002 and Fraser's 2005 publication dates in its Preliminary Response of Patent Owner in IPR2021-00402. Ex. 1053, 8.

publicly available within a few days or at most 2 to 3 weeks after February 15, 2005. Ex. 1002, ¶¶295-296; Ex. 1075. As discussed in Section X, the '231 patent is not entitled to a priority date earlier than the non-provisional filing date of March 22, 2006. Each of November 2004 and February 2005 is more than one year prior to that date. *Id.* Thus, Fraser qualifies as prior art under pre-AIA 35 U.S.C. § 102(b) and post-AIA 35 U.S.C. § 102(a)(1). Ex. 1002, ¶296.

Andya was published on August 16, 2001, which is more than one year prior to the '231 patent's earliest possible priority date and qualifies as prior art under pre-AIA 35 U.S.C. § 102(b) and post-AIA 35 U.S.C. § 102(a)(1). Ex. 1002, ¶310.

3. Wulff and Fraser Taught Buffered Formulations Containing the VEGF Trap Protein, Polysorbate 20, and Sucrose Having Strong VEGF Binding Affinity and Biological Potency, and the Claimed Less Than 3% Degradation

Wulff evaluated the VEGF TrapR1R2 protein and its biological activity in inhibiting VEGF. Ex. 1002, ¶¶127-129, 285; Ex. 1004, 2797, Abstract. Wulff describes the VEGF antagonist of the '231 patent[10]:

[10] The VEGF Trap of the '231 patent was well known in the prior art. Ex. 1002, ¶¶118-142. Wulff discloses in footnote 1 (p. 2798) that the VEGF Trap, including its molecular structure and how it was created, are described in PO's publication WO 00/75319 ("Papadopoulos," Ex. 1016), published December 14, 2000, which

> The VEGF Trap R1R2 used in these experiments is a recombinant chimeric protein comprising portions of the extracellular, ligand binding domains of the human VEGF receptors Flt-1 (VEGF-R1, Ig domain 2) and KDR (VEGF-R2, Ig domain 3) expressed in sequence with the Fc portion of human IgG (Fig. 1). The presence of the Fc

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disclosed the exact same VEGF Trap disclosed and claimed in the '231 Patent. Ex. 1002, ¶¶118-121. Papadopoulos disclosed "VEGFR1R2-FcΔC1(a)," having SEQ ID NO: 4 of the '231 Patent and now known as "aflibercept" as admitted by PO. Ex. 1016, 26:12-25; Ex. 1057, 2-7; Ex. 1002, ¶120. The nucleotide and amino acid sequences of VEGFR1R2-FcΔC1(a) are provided in Papadopoulos Figs. 24A-24C. Ex. 1016, 22:1-2. The amino acid sequence of VEGFR1R2-FcΔC1(a) in Papadopoulos is 100% identical to SEQ ID NO: 4 of the '231 Patent. Ex. 1002, ¶120, Appendix B. As known in the prior art, the complete SEQ ID NO:4 includes, *inter alia*, a signal peptide that is removed and a C-terminal lysine clipped during protein production. *See* Ex. 1016, 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); Ex. 1002, ¶¶120, 289. Accordingly, amino acids 27-457 of SEQ ID NO:4 published in 2000 are aflibercept. Ex. 1002, ¶¶130-131. PO also published the same sequence on August 8, 2002, in Figs 24A-24C of Xia. Ex. 1018; Ex. 1002, ¶¶130-131.

> domain results in homodimerization of the recombinant protein, thereby creating a high affinity (KD1–5pM) VEGF Trap.[1] The VEGF trap was expressed in CHO cells and was purified by protein A affinity chromatography followed by size-exclusion chromatography. The specificity of VEGF binding and the affinity to VEGF of VEGF Trap R1R2 were determined by Biacore (Uppsala, Sweden).

Ex. 1004, 2798.

Wulff also teaches a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20")[11], a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." *Id*.[12] Wulff discloses that a dose of 25 mg/kg of the VEGF Trap was injected subcutaneously into marmosets. Ex. 1002, ¶292; Ex. 1004, 2798. Thus, a POSA

[11] Tween 20 is a commercial brand name for polysorbate 20. Ex. 1002, ¶330.

[12] A VEGF Trap formulation containing the same excipients in the same concentrations was tested in the '231 patent ("VGT-FS405") and "less than about 1% degradation was detected after 3 years of storage at 2-8°C." Ex. 1001, 10:4-14. Data are also disclosed related to the same formulation's ability to inhibit biological activity of human VEGF as measured by a mouse Baf/3 VEGFR1/EpoR cell line relative to a reference VEGF IC_{50} standard and ability to bind VEGF at a percent relative binding to a reference VEGF IC_{50} standard, after storage at 5°C for 3 months. *Id*. at 10:66-11:30.

would have understood that the computed concentration of the VEGF Trap injected subcutaneously in Wulff was 5 to 12.5 mg/ml. *Id.* Wulff discloses that the VEGF TrapR1R2 was administered subcutaneously (sc) to the monkeys "[t]o inhibit vascular endothelial growth factor (VEGF)," (Ex. 1004, Abstract), and that "VEGF Trap R1R2 may be more efficient in inhibiting VEGF, because it contains an additional domain of the second VEGF receptor KDR." *Id*. at 2804; Ex. 1002, ¶293. Thus, a POSA reading Wulff would have understood that it discloses that the VEGF Trap of the '231 patent was found to bind to VEGF with high affinity (1-5 pM) and to potently inhibit the activity of VEGF. Ex. 1002, ¶335. Indeed, the same information was published in 2002 in PO's "Holash" article (Ex. 1009), which was also cited as a description of the aflibercept protein in PO's Patent Term Extension application. Ex. 1002, ¶335; Ex. 1057, 5-7.

Fraser is titled "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function." Ex. 1002, ¶296; Ex. 1003, 1114. Fraser lists PO, Regeneron, as employer of at least one of the authors. Ex. 1002, ¶297; Ex. 1003, 1114.

Fraser's study evaluated the VEGF TrapR1R2 protein and its biological activity in inhibiting VEGF. Ex. 1002, ¶298; Ex. 1003, 1114. Fraser conducted the study examining transient inhibition of VEGF on pituitary-ovarian function in

which macaques were given an injection of the VEGF TrapR1R2. Ex. 1002, ¶298; Ex. 1003, 1114. In Fraser's experiments, "VEGF was inhibited by administration of VEGF TrapR1R2, a recombinant, chimeric protein comprising Ig domain 2 of human VEGF-R1 and Ig domain 3 of human VEGF-R2, expressed in sequence with the human Fc." Ex. 1002, ¶300; Ex. 1003, 1115. It is indisputable that the VEGF TrapR1R2 disclosed in Fraser is claimed in the '231 Patent. *First*, Fraser specifically discloses Regeneron's VEGF Trap: "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." Ex. 1002, ¶299; Ex. 1003, 1114. *Second*, as explained in the Tarantino Declaration, PO published the sequence of aflibercept in a series of publications starting in 2000 and admitted in its patent term extension application for the Papadopoulos U.S. patent that aflibercept is "also known as VEGF trap, VEGF-trap, VEGF Trap-EYE and VEGF-TRAP$_{R1R2}$" and referred to the same amino acid sequence in Fig. 24A-24C of Papadopoulos and Xia. Ex. 1002, ¶326. *Third*, Fraser also refers to Wulff as reference 17 and Holash as reference 21. Ex. 1002, ¶¶301- 304; Ex. 1003, 1114, 1119. *Fourth*, PO submitted a § 1.131 Declaration ("Dix '546"; Ex. 1054) during prosecution of the '065 application, which issued as U.S. Patent No. 8,110,546 (the first issued patent in the '231 patent's priority

chain), identifying one of the formulations as Fraser's formulation: "24.3 mg/ml VEGF Trap protein, 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 20% sucrose, and 0.1% polysorbate-20, pH 6.05, ***which is the actual lot and formulation used in Fraser***." Ex. 1054, 2 (citing Ex. C) (emphasis added); Ex. 1002, ¶306. This evidence helps "to elucidate what the prior art consisted of." *Hospira, Inc. v. Fresnius Kabi USA, LLC,* 946 F.3d 1322, 1330 (Fed. Cir. 2020); *Monsanto Tech. LLC v. E.I. DuPont de Nemours & Co.*, 878 F.3d 1336, 1345 (Fed. Cir. 2018) (allowing "non-prior art data" to be used to support inherency); *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (finding that the prior art need not recognize the inherent property). Thus, PO cannot credibly dispute that Fraser disclosed the VEGF TrapR1R2 protein having the sequence claimed in the '231 patent.

In addition, there can be no dispute that the VEGF TrapR1R2 of Fraser possesses the same bioavailability and pharmacokinetic properties as the VEGF Trap formulations claimed by the '231 patent. Fraser, like Wulff, discloses that "VEGF TrapR1R2 exhibits greater affinity for VEGF-A (affinity constant ~1 pM) as well as improved bioavailability and pharmacokinetic properties (21)." Ex. 1002, ¶¶302, 335; Ex. 1003, 1115. Moreover, PO has implicitly acknowledged that Fraser's formulation would possess the claimed stability properties. During prosecution of the '065 application, the examiner rejected claims directed to

phosphate-citrate buffered VEGF Trap formulations as obvious of Fraser, explaining that "the composition is identical," and "[t]he limitations regarding properties after storage are dictated by the components of the composition and thus intrinsic to it." Ex. 1002, ¶337; Ex. 1055, 3-6. PO did not challenge that the properties would be intrinsic to the formulation, asserting instead that they could antedate Fraser's publication. Ex. 1002, ¶337; Ex. 1056, at 3-4. These statements further support a POSA's understanding that Fraser's formulation shares the same stability properties as the formulation tested in the common specification and alleged to have the claimed stability, potency, and binding characteristics. Ex. 1002, ¶338; Ex. 1001, 11:4-14, 12:1-30.

Thus, Wulff and Fraser disclosed a formulation comprising the claimed VEGF fusion protein, a buffer, a polysorbate (polysorbate 20), a sugar (sucrose), and PO has admitted—and the '231 patent provides data supporting—that the disclosed formulation possesses the claimed stability, potency, and binding functionalities.

4. Andya Taught that Histidine was an Exceptional and Useful Buffer for Generating Protein Formulations Having Higher Concentrations with Low Degradation

Although Wulff and Fraser did not disclose a buffer comprising histidine, it was well-known, long before the '231 patent's earliest possible priority date, that a histidine buffer was a suitable and preferred buffer for stabilizing protein

formulations, particularly at higher concentrations. Ex. 1002, ¶322. For example, Andya specifically discloses that a "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, preferable 3-10 times higher and most preferable 3-6 times higher) than the protein concentration in the pre-lyophilized formulation," (Ex. 1005, ¶[0008]), and that "the preferred buffer is histidine in that, as demonstrated below, this can have lyoprotective properties" (*Id*. ¶96). Ex. 1002, ¶311. The buffer concentrations disclosed in Andya also overlap those used in Wulff/Fraser and those claimed in the '231 patent. *Id*. ¶314.

Andya does not limit its teachings to only specific proteins and instead discloses that its teachings are applicable for formulating various types of proteins and protein receptors, including antibodies and biologically active fragments or variants of any of the disclosed proteins including, but not limited to VEGF in paragraphs [0042] and [0044], as well as anti-VEGF antibodies in paragraph [0102]. Ex. 1002, ¶311; Ex. 1005. While PO may argue that Andya does not explicitly reference VEGF Trap fusion proteins, a POSA reading Andya would have understood that Andya does not limit its disclosures to specific proteins, but rather provides a list that POSAs would have recognized to be inclusive of many therapeutic proteins. Ex. 1002, ¶320. This understanding is further buttressed by similar disclosures in other contemporaneous publications and multiple FDA

approved products. Ex. 1002, ¶157; Ex. 1033; Ex. 1039. This case is not about a novel fusion protein or a novel formulation because the claimed protein and its amino acid sequence were already known, as were details about purifying and formulating it, as well as the well-known sugar/polysorbate/histidine buffer system. Ex. 1002, ¶341-360. The Examiner's failure to recognize that all elements of the claimed formulations were known and obvious to a POSA constitutes a material error.

A POSA would have also known that there was a small group of commonly used buffers for protein formulations, (*see* Ex. 1005, ¶[0096]), and known that the protein had been formulated at pH 6 by Fraser, which is squarely within the buffering range of histidine. Ex. 1002, ¶¶342-345; Ex. 1033 ¶58; Ex. 1005, ¶[0096]; Ex. 1030, 297; Ex. 1031, 527. Moreover, numerous FDA-approved proteinaceous therapeutics contained a buffer comprising histidine, and applicability of histidine buffers to various types of proteins was well-known. Ex. 1002, ¶345; Ex. 1040; Ex. 1041; Ex. 1042; Ex. 1043.

Andya also discloses that histidine was a "particularly useful buffer" because it was exceptionally effective for preventing aggregation, providing data to support the disclosure. Ex. 1005, ¶[0160], FIGS. 9-10; Ex. 1002, ¶357. For example, FIG. 10 reflects that histidine buffer reduced aggregation and was effective at stabilizing formulations at pH 6. Ex. 1005; Ex. 1002, ¶315. Moreover,

when combined with a stabilizing agent comprising a sugar, an amino acid or both (*e.g.*, sucrose, trehalose, mannitol, and/or glycine), Andya's formulations demonstrated high stability and lacked degradation as shown in Tables 2, 3, 5, 6, and 9. Ex. 1002, ¶316; Ex. 1005. Indeed, FIG. 17 shows a combination of a histidine buffer and a sugar, *i.e.*, sucrose or trehalose has less than 1.5% aggregation throughout the entire 40 week test period. Ex. 1002, ¶317; Ex. 1005, FIG. 17, ¶[0160].

Like Wulff/Fraser, Andya also discloses that, in addition to the buffer, the protein formulation should contain sucrose and a polysorbate such as polysorbate 20 (Tween 20™) to reduce aggregation and/or reduce particulate formation. Ex. 1005, ¶¶[0014], [0052], [0097], [0123], [0126], [0128], [0136], [166], [0175], [0176], Tables 3, 6, 9, and 10; Ex. 1002, ¶318. Indeed, a POSA reading Andya would have understood that histidine and sucrose with polysorbate 20 significantly reduces the number of particles in order to meet US Pharmacopeia (USP) specification for small volume injections. Ex. 1002, ¶318; Ex. 1005, ¶¶[0175]-[0176].

5. It Would Have Been Obvious to a POSA to Combine Wulff or Fraser and Andya To Arrive At the Formulation Claimed in the '231 Patent

The claimed VEGF Trap, its formulation with a sugar, a polysorbate, and a buffer with buffering capacity at pH 6 including histidine, as well as the excipient

concentrations were well-known in the art. Moreover, POSAs would have combined them with a reasonable expectation of success and without change to their respective functions. The primary difference between Fraser/Wulff and the formulation of the '231 patent's independent claims is that the buffer of Wulff/Fraser did not contain some amount of histidine. Ex. 1002, ¶321-22.

Before 2005, however, the prior art as a whole recognized multiple advantages and suggestions to use the well-known histidine buffer system exemplified in Andya in proteinaceous therapeutic formulations. *Id.* The prior art recognized that histidine was one of a small group of commonly used buffers for stabilizing proteinaceous therapeutic formulations and had been used in multiple FDA approved products and particularly useful for formulation high concentration protein formulations. *Id.*; Ex. 1005, ¶[0096].

Specifically, it would have been obvious to use histidine because of its usefulness in preventing aggregation and generating a stable formulation having a protein concentration, which is significantly higher than the protein concentration in the pre-lyophilized formulation, improving its lyoprotective properties, and improving long term storage stability. Ex. 1002, ¶322; Ex 1005; Ex. 1033; Ex. 1039. It would have been obvious to use Andya's histidine buffer in the Fraser/Wulff formulations for the additional reasons that: (1) its pK_a provides maximum buffering capacity at pH 6 (the same as Fraser's formulation), (2) it had

suitable pK_a and buffering capacity for the VEGF TrapR1R2 protein having a pI of approximately 8, (3) it contributes less to osmolarity than Fraser/Wulff's phosphate-citrate buffers, (4) phosphate-citrate buffers were known to cause painful reactions when injected subcutaneously in contrast to histidine buffer, and (5) regulatory agencies had repeatedly approved histidine-buffered proteinaceous therapeutic formulations. Ex. 1002, ¶322. Each point is addressed below.

There was motivation to use Andya's histidine buffer in Wulff/Fraser's formulation because Andya teaches that it can be used to generate a stable formulation having protein concentrations 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 and has lyoprotective properties. Ex. 1002, ¶311; Ex. 1005, ¶[0096]. Given that Fraser formulation's VEGF Trap concentration was 24.3 mg/ml, a POSA would have been motivated to generate a stable formulation having a significantly higher protein concentration, *e.g.*, by following Andya's teachings to lyophilize and reconstitute in histidine buffer so as to increase the concentration by at least 2-fold (*e.g.*, from ~25 to ~50 mg/ml). Ex. 1002, ¶354.

Even more, a POSA would have noted that Fraser's formulation was stored at 4°C and discarded within 2 weeks (Ex. 1003, 1115), and would have been motivated to use histidine to generate a formulation with the longer storage

stability as disclosed by Andya's disclosure of histidine-buffered formulations with long-term storage stability of "at least 2 years." Ex. 1002, ¶356; Ex. 1005, ¶[0049].

Moreover, a POSA would have wanted to retain or improve the stability, binding, and potency of the Wulff/Fraser VEGF TrapR1R2, and would have been motivated to use histidine based on Andya's teaching that it was especially good at preventing degradation including aggregation. Ex. 1002, ¶¶322-324; Ex. 1005, ¶[0160], FIGS. 9-10. This usefulness was further supported by a POSA's knowledge of FDA-approved proteinaceous therapeutic formulations using histidine, where there are regulatory requirements requiring such stability. Ex. 1002, ¶351-53.

In addition, a POSA would have known that Andya's histidine buffer has a lower osmolality than Wulff/Fraser's phosphate-citrate buffer, and thus would allow for the inclusion of additional excipients (such as more stabilizer) and avoid the need for dilution before injection, which is particularly important for small volume injectable products. *Id.* ¶322. A POSA would have been further motivated to alter the Wulff/Fraser phosphate-citrate buffer because it was known to cause painful reactions in subcutaneous injection whereas histidine does not. *Id.* ¶¶322, 355. This would have been especially relevant to formulating a higher

concentration VEGF TrapR1R2 formulation, which can advantageously be administered subcutaneously rather than intravenously. *Id.* ¶¶322, 354.

POSAs were likewise very familiar with the combination of histidine and the other excipients of Wulff/Fraser, including a sugar such as sucrose or trehalose and polysorbate 20, to formulate stable protein formulations. *Id.* ¶351 (listing numerous FDA-approved proteinaceous therapeutics containing the same combination of excipients.) The Federal Circuit has recognized that a POSA would have been motivated to use familiar excipients that had already been accepted by regulatory agencies to be safe for use in such proteinaceous therapeutic formulations. *See Bayer Pharma AG v. Watson Labs. Inc.*, 874 F.3d 1316, 1328-29 (Fed. Cir. 2017) (explaining that prior art "expresses a clear motivation" where common excipients were already used in FDA-approved drugs).

A POSA would have had a reasonable expectation of success in using Andya's histidine buffer with the Fraser/Wulff VEGF Trap formulations. Ex. 1002, ¶357. Histidine's pK_a of approximately 6.0 has optimal buffering capacity at pH 6.0 (the same as Fraser). *Id.* ¶358; Ex. 1032, ¶[0050]. A pH of 6.0 is likewise an optimal pH for these VEGF Trap formulations because it is sufficiently below

the isoelectric point of the VEGF Trap (which is approximately 8.2),[13] and would thus render the protein soluble and reduce its aggregation. *Id.* ¶¶322, 344; Ex. 1035, 11.

Moreover, Andya disclosed that histidine buffer could be used successfully with the other excipients (sucrose and polysorbate 20) of Wulff/Fraser's formulation. *Id.* ¶322-23. A POSA would further have had a reasonable expectation of achieving a formulation that maintains the stability, potency, and binding properties of Wulff/Fraser's formulation using this combination of ingredients given the numerous other FDA-approved protein therapeutics containing the same combination of excipients, and in view of Andya's teaching that histidine has an exceptional ability to act as a lyoprotectant and prevent degradation. *Id.* ¶¶356-360.

If PO argues that it was unpredictable what effect the addition of histidine would have in Wulff/Fraser's formulation, then PO's argument will confirm that the '231 patent claims lack written description support and are not enabled. *Id.* ¶¶369-371. As discussed in Sections XI.A.-B., above, there is little disclosure in the '231 patent specification beyond what was in the prior art (indeed, the '231

[13] As calculated by Petitioner's expert Dr. Tarantino, using the prior art Expasy bioinformatics suite. Ex. 1002, ¶154; Ex. 1036; Ex. 1038.

patent specification is formatted nearly identically to that of Andya), and not a single disclosed formulation falls within the scope of the claims. If PO alleges that the term VEGF TrapR1R2 in Wulff/Fraser encompasses a number of different proteins having different properties, then PO's argument will confirm that the '231 patent claims lack written description support and are not enabled as they indisputably encompass an unbounded genus of different proteins having different properties, all but one of which were not made, described, or tested. *Id*. Thus, to the extent PO alleges the broadly claimed formulations are not obvious over the prior art, they are not adequately supported and enabled—and certainly not across the full scope of the claims—by the '231 patent disclosure and are invalid under 35 U.S.C. § 112.

There are no unexpected results in the claimed stability, potency, and binding limitations as it is indisputable that—to the extent they are adequately supported by the specification—these were all properties present in Wulff/Fraser's formulation (as evidenced by demonstration of these properties of that formulation in the '231 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.*, 946 F.3d at 1332 (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."). Moreover, PO certainly

has not demonstrated unexpected results commensurate with the broadly claimed formulations. Ex. 1002 ¶374.

As set forth above and explained in detail in Dr. Tarantino's Declaration, although Wulff and Fraser did not disclose a buffer comprising histidine, it was a well-known buffer long before the '231 patent's earliest possible priority date and its multiple advantages were also well-known and would have motivated a POSA to use histidine buffer in Wulff/Fraser's formulation. Ex. 1002 ¶¶357-360. Thus, Wulff or Fraser in view of Andya renders obvious each of independent claims 1, 27, and 31 of the '231 patent. *Id*. ¶360.

6. Claims 2, 28, and 32

Andya discloses and exemplifies formulations containing 5, 10, and 20 mM histidine buffer throughout, including in Tables 2-3, 5-6, 10 and paragraphs [0174]-[0175]. Ex. 1002 ¶361; Ex. 1005. Thus, Wulff or Fraser in view of Andya renders obvious "said buffer comprises 5-50 mM histidine" by disclosing species in the claimed range. Ex. 1002 ¶361.

7. Claims 3, 44, and 58

Andya discloses and exemplifies formulations containing 10 mM histidine throughout, including in Table 2, Fig. 9, and paragraphs [0029] and [0126]. Ex. 1002 ¶362; Ex. 1005. Thus, Wulff or Fraser in view of Andya renders obvious "said buffer comprises about 10 mM histidine." Ex. 1002 ¶362.

8. Claims 4, 45, and 59

Andya discloses and exemplifies formulations containing histidine buffer at a pH of 6.0 throughout. Ex. 1002 ¶363; Ex. 1005. Thus, Wulff or Fraser in view of Andya renders obvious "said buffer is at a pH of about 6.0-6.5" by disclosing species in the claimed range. Ex. 1002 ¶363.

9. Claims 6 and 7

Each of Wulff and Fraser discloses a formulation containing 100 mM sodium chloride. Ex. 1002 ¶364; Ex. 1004, 2798; Ex. 1003, 1115;. Thus, Wulff or Fraser in view of Andya renders obvious "said formulation further comprises a tonicity agent" and "wherein said tonicity agent is sodium chloride." *Id.* ¶364.

10. Claims 8, 9, 41, and 42

Each of Wulff and Fraser discloses a formulation containing 0.1% polysorbate 20. Ex. 1002 ¶365; Ex. 1004, 2798; Ex. 1003, 1115. Thus, Wulff or Fraser in view of Andya renders obvious that "wherein said organic co-solvent comprises 0.1-0.5% polysorbate, " "wherein said organic co-solvent comprises 0.05-0.15% polysorbate 20," "wherein said organic co-solvent comprises 0.003-0.15% polysorbate," and "wherein said organic co-solvent comprises polysorbate 20" by disclosing species, including in the claimed ranges. *Id.* ¶365.

11. Claims 10-11

Each of Wulff and Fraser discloses a formulation with 20% sucrose. Ex. 1002 ¶366; Ex. 1004, 2798; Ex. 1003, 1115. Thus, Wulff or Fraser in view of Andya

renders obvious "said stabilizing agent comprises a sugar" and "said sugar is selected from group consisting of dextrose, ribose, fructose, mannitol, inositol, sorbitol, trehalose, sucrose, and lactose" by disclosing species of the claimed genera. *Id.* ¶366.

12. Claims 18-19

Each of Wulff and Fraser discloses a formulation containing 0.1% polysorbate 20 and 100 mM sodium chloride. Ex. 1002 ¶367; Ex. 1004, 2798; Ex. 1003, 1115. Thus, Wulff or Fraser in view of Andya renders obvious the "formulation of claim 9, wherein said formulation further comprises a tonicity agent" and the "formulation of claim 18, wherein said tonicity agent is sodium chloride" by disclosing species of the claimed genera. *Id.* ¶367.

13. Claims 20-21

Each of Wulff and Fraser discloses a formulation containing 0.1% polysorbate 20 and 20% sucrose. Ex. 1002 ¶368; Ex. 1004, 2798; Ex. 1003, 1115. Thus, Wulff or Fraser in view of Andya renders obvious the "formulation of claim 9, wherein said stabilizing agent comprises a sugar" and the "formulation of claim 20, wherein said sugar is selected from group consisting of dextrose, ribose, fructose, mannitol, inositol, sorbitol, trehalose, sucrose, and lactose" by disclosing species of the claimed genera. *Id.* ¶368.

14. Claims 29-30

Independent claim 27 did not specify any storage time period for measuring the potency of the VEGF antagonist fusion protein. Ex. 1002 ¶369. Claims 29 and 30 specify that said percent relative potency of at least 75 is achieved "after 1 month" and "after 24 months" of storage at 5° C, respectively. *Id.* As discussed in Section XI.A., the '231 patent did not disclose any formulation within the scope of the claims for biological potency. *Id.* Instead, PO only tested formulations outside the scope of the claims, including formulations containing the same excipients in the same concentrations as the Wulff and Fraser formulation. Ex. 1002 ¶369; Ex. 1001, 10:56-12:30 (Example 5). The data are reported in Table 9, demonstrating that the formulation meets the claimed limitation at both 1 month and 24 months (to the extent any formulation can satisfy these limitations given the §112 issues addressed in Sections XI.A.-C.). *See id.* ¶370. Claiming a composition's inherent property does not render a claim to the composition nonobvious. *Hospira Inc.*, 946 F.3d at 1332-33; *see also Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999). ("discovery of a previously unappreciated property of a prior art composition … does not render the old composition patentably new …..". Thus, Wulff or Fraser in view of Andya renders obvious the subject matter of claims 29-30. Ex. 1002 ¶370.

Moreover, the claimed potency of at least 75 for up to 24 months appears to be derived from the Wulff/Fraser phosphate-citrate formulation, rather than a histidine formulation. *Id.* To the extent PO argues that the effect of adding histidine to the Wulff/Fraser formulation was unpredictable, it will confirm that the specification lacks written description support for the subject matter of claims 27-30 because no formulation tested for potency falls within the claims' scope, and thus there are no supporting data demonstrating possession of the broadly-claimed genus of formulations having the claimed potency. *Id.*

15. Claim 43

Andya discloses and exemplifies formulations containing 5, 10, and 20 mM histidine buffer throughout, including in Tables 2-3, 5-6, 10 and paragraphs [0174]-[0175]. Ex. 1002 ¶371; Ex. 1005. Thus, Wulff or Fraser in view of Andya renders obvious "said buffer comprises 5-50 mM histidine" by disclosing species in the claimed range. Ex. 1002 ¶371. If PO argues that it the effect of adding histidine to the Wulff/Fraser formulation was unpredictable, it will confirm that the specification lacks written description support for the subject matter of claim 43 because no formulation tested for potency falls within the claims' scope, and thus there are no supporting data demonstrating possession of the broadly-claimed genus of formulations having the claimed potency. *Id.*

XII. CONCLUSION

For the reasons explained above, Petitioner respectfully requests institution of post-grant review of the ’231 patent Challenged Claims on the grounds presented herein, and cancellation of those claims in a final written decision.

Date: September 7, 2021

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CERTIFICATE OF COMPLIANCE

I, the undersigned, certify that the above Petition for Post-Grant Review complies with the applicable type-volume limitations of 37 C.F.R. § 42.24(a)(1)(ii). Exclusive of the portions exempted by 37 C.F.R. **§** 42.24(a), this Petition, including footnotes, contains 18,579 words, as counted by the word count function of Microsoft Word 2010 and as counted manually with respect to the included figures with annotations. This is less than the limit of 18,700 words as specified by 37 C.F.R. § 42.24(a)(1)(ii).

Date: September 7, 2021

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4) and 42.205, the undersigned certifies that on September 7, 2021, a complete and entire copy of the foregoing **Petition for Post-Grant Review of U.S. Patent No. 10,857,231 Under 35 U.S.C. §§ 321-329 and 37 C.F.R. § 42.200 et seq.**, along with supporting Exhibits 1001-1077 and Power of Attorney, were served via Federal Express overnight courier on the Patent Owner, by serving the attorneys of record at the following correspondence address of record for the subject patent:

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