Paper No. 6
Filed: August 11, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

BOEHRINGER INGELHEIM INTERNATIONAL GMBH,
Patent Owner.

Case PGR2022-00037
Patent No. 11,078,265

PATENT OWNER'S PRELIMINARY RESPONSE

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TABLE OF ABBREVIATIONS

Abbreviation	Description
’265 patent	U.S. Patent No. 11,078,265
AIA	America Invents Act
Boehringer or Patent Owner	Boehringer Ingelheim International GmbH
Board or PTAB	Patent Trial and Appeal Board
FDA	U.S. Food and Drug Administration
Italicized and Bold	Emphasis added unless indicated otherwise
POSA	person of ordinary skill in the art
Sandoz or Petitioner	Sandoz Inc.
USPTO or Office	U.S. Patent and Trademark Office

EXHIBIT LIST

Exhibit	Description
2001	RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS: THEORY AND PRACTICE (John F. Carpenter & Mark C. Manning eds., 2002)
2002	Awotwe-Otoo et al., *Quality by Design: Impact of Formulation Variables and Their Interaction on Quality Attributes of a Lyophilized Monoclonal Antibody*, 438 INT. J. PHARM. 167 (2012)
2003	Chen et al., Influence of Histidine on the Stability and Physical Properties of a Fully Human Antibody in Aqueous and Solid Forms, 20 PHARM. RES. 1957 (2003)
2004	*Momenta Pharms., Inc. v. Bristol-Myers Squibb Co.*, IPR2015-01537, Ex. 1019 (Transcript of Deposition of Dr. Alexander Klibanov)
2005	Risankizumab: Statement on a Nonproprietary Name Adopted by the USAN Council (USAN) (Mar. 29, 2017)
2006	*Amag Pharms., Inc., v. Sandoz Inc.*, No. 3:16-cv-01508-PGS-LHG, Dkt. No. 53-1 (D.N.J. Mar. 10, 2017)
2007	Humira® Prescribing Information (Rev. May 2012)

I. INTRODUCTION

Petitioner challenges claims 7-10, 14-16, 19-22, 27, and 28 of the '265 patent, directed to stable, isotonic, liquid aqueous pharmaceutical formulations, in a narrow pH range, comprising a specific sequence-defined antibody (hereinafter "risankizumab") and a limited set of excipient categories. The '265 patent discloses multiple exemplary formulations representative of these excipient categories and includes empirical data establishing stability.

Petitioner raises two related challenges: (1) written description and (2) enablement. Both grounds hinge on Petitioner's argument that the challenged claims are "broad," encompassing "millions of potential formulations" due to the recitation of "generic" categories of excipients. Petitioner argues that the specification does not adequately describe or enable the claims because preparing "stable" formulations was unpredictable. Substantially similar arguments were overcome during prosecution.

The Board should reject Petitioner's arguments and deny institution for at least four independent reasons. *First*, Petitioner failed to comply with 37 C.F.R. § 42.204(b)(3)-(4), which requires the petition to explain how the challenged claims should be construed. Although both of its grounds hinge on the claim term "stable," Petitioner has not proffered an actual construction. Under the rubric of claim construction, Petitioner instead discusses the scope of the independent claims,

arguing (wrongly) that they must encompass two subgenera of formulations that are "stable" following storage under certain conditions. That does not explain what "stable" means. Further, Petitioner's importation of storage conditions from an example in the specification and a dependent claim disregards fundamental principles of claim construction—an error that infects the entire Petition. As set forth below, Petitioner offers no evidence that the challenged claims are unpatentable when "stable" is properly construed. For this reason alone, the Petition is deficient, and denial is warranted.

Second, regardless of how "stable" is construed, Petitioner's written description and enablement arguments are fundamentally flawed. Instead of focusing on the claimed invention, Petitioner premises its allegations of unpredictability on formulations involving other antibodies and even other proteins. Although the claims are limited to risankizumab, Petitioner identifies ***no risankizumab formulation*** meeting the structural limitations of the claims that is unstable. Petitioner also disregards the guidance provided by the disclosed formulations, which vary substantially within the claimed excipient categories. Further, instead of focusing on what is claimed—liquid, aqueous, "antibody" formulations—Petitioner's calculations that the claims encompass "millions of potential formulations" are premised on excipients ***used for lyophilized formulations, small molecules, and other unrelated drug types***. Because Petitioner

fails to make the necessary threshold showing that it is more likely than not that any challenged claim is unpatentable, the Board should deny institution.

Third, Petitioner's unpatentability arguments are substantially the same as those considered by the Office and overcome during prosecution, repeating verbatim arguments made by the Examiner in rejecting the claims under Section 112. In an effort to avoid discretionary denial, Petitioner ramps up the rhetoric, repeatedly and wrongly alleging that Patent Owner "mischaracterized" relevant authority, *Fresenius*, and further that the Examiner "misunderstood" the scope of the issued claims and the supporting disclosure. But Patent Owner ***submitted*** the *Fresenius* decision to the Office. Moreover, the record reveals that Patent Owner correctly characterized *Fresenius*, and that the Examiner carefully and independently assessed its relevance. Petitioner's "material error" arguments at most amount to a strained attempt to distinguish *Fresenius*—highly analogous authority carefully vetted in prosecution that supports denial of institution. The Board should therefore exercise discretion under 35 U.S.C. § 325(d) and deny institution.

Fourth, Petitioner fails to establish that the '265 patent, which issued from a transitional application, is eligible for post-grant review. Petitioner alleges that the provisional application fails to adequately describe and enable claim 14 for the same reasons as the '265 patent, arguing that it contains no more disclosure than the patent

itself. Because Petitioner's written description and enablement challenges lack merit, its eligibility arguments also fail.

For each of these reasons, and as detailed below, denial of institution is warranted.

II. BACKGROUND

A. Monoclonal Antibody Formulation Development as of 2012

Formulation development is a critical part of developing a therapeutic monoclonal antibody. Given their proteinaceous nature, antibody drugs face drug stability issues during manufacturing, storage, and delivery to patients. One primary objective for designing a monoclonal antibody formulation is to identify appropriate excipients and formulation pH that can stabilize the antibody's native structure. EX1014, 14; EX2001, 10, 13 (Table 6), 14 (Table 7).[1]

Each antibody has unique chemical and physical properties conferred by its distinct heavy- and light-chain amino acid sequences. EX1008, 690. From a formulation perspective, this structural diversity results in significant unpredictability across antibodies with different sequences, as each antibody

[1] Citations refer to the original page numbering of each exhibit except for references that do not have any pagination in their original form. Citations to the latter refer to the stamped-on page numbers.

displays unique chemical and physical properties that control its rate of degradation. EX1008, 690; EX1014, Abstract, 14. As Petitioner's expert Dr. Klibanov explains, "a POSA could not legitimately assume that a formulation that results in a satisfactory stability for one antibody also could be successfully used for another antibody."[2] EX1002 ¶ 29.

Based on the evidence of record, twenty-one therapeutic monoclonal antibodies had been approved by the FDA as liquid aqueous formulations by 2012 (excluding conjugates). *See infra* App'x A. These products provided some guidance for selecting potential excipients, including detergents, tonicity agents, and buffers. *See, e.g.*, EX1010, 523 (Table 2), 526 ("Successful examples of marketed mAbs may provide important information for new mAbs currently under investigation or in clinical research."); EX1014, 1, 2-4 (Table 1); EX1008, 697 (Table 1). Petitioner and its expert Dr. Klibanov state that various detergents, tonicity agents, and buffers were each well-known by 2012 for liquid aqueous antibody formulations. *See, e.g.*, Pet. at 9-11, 13; EX1002 ¶¶ 39, 47, 51, 53, 57, 62.

Detergents (also called surfactants or surface-active compounds) are amphipathic molecules that prevent surface-induced degradation. EX1042, 300-01.

[2] For purposes of this Preliminary Response, Patent Owner does not dispute Petitioner's definition of a POSA. *See* Pet. at 33.

At sufficient concentrations (typically around the detergent's critical micellar concentration), a surface layer of detergent molecules prevents protein molecules from adsorbing at the interface. *Id.* As of 2012, only two detergents, polysorbate 20 and polysorbate 80, had been used in FDA-approved liquid aqueous monoclonal antibody formulations. *See infra* App'x A.

Tonicity agents provide isotonicity to monoclonal antibody formulations (i.e., the formulation has the same concentration of dissolved particles as human plasma, such that it is suitable for injection). EX1042, 296, 298-300. Tonicity agents are generally classified as ionic (such as NaCl) or non-ionic (such as sorbitol) based on whether the agent dissolves into charged particles in solution. *See id.* As of 2012, only a handful of tonicity agents had been used in approved liquid aqueous monoclonal antibody formulations. *See infra* App'x A. Because isotonicity was a goal for many liquid aqueous antibody formulations, the range of concentrations for tonicity agents were constrained. *See id.*; EX1042, 299.

Buffers are added to antibody formulations to adjust and stabilize pH. EX1015, 294; EX1042, 296, 297. By 2012, it was understood that pH was often critical for antibody stability, and that maximal stability was generally observed in a narrow pH range. EX1042, 297. It was also understood that each buffer can maintain pH only over a particular range; thus, a target pH range limited the available buffers suitable for a liquid antibody formulation. *Id*., 297 (Table 2); EX1015, 295-

96 (Table VII). Organic acids and phosphates were frequently employed as buffers in monoclonal antibody formulations. *See infra* App'x A. It was also known that some antibodies could be formulated without a buffer due to their self-buffering capacity, and that such antibodies could be formulated without an additional buffering system once their self-buffering capacity was determined. *See, e.g.*, EX1002 ¶ 53; EX1016, 3052, 3064; EX1018, 491.

B. Tools Available to Assist with Formulation Development

By 2012, various tools were available for designing and testing formulation stability. For example, fractional factorial design could be applied to screen the main effects of several variables on a particular monoclonal antibody using a limited set of experiments, rather than testing every possible excipient at each possible concentration in a combinatorial fashion. *See* EX2002, 169, 172, Table 2; EX2003, Abstract, 1953 (Table I). High-throughput screening ("HTS") techniques were also employed to test a variety of excipients with a given antibody in parallel, including in accelerated stability studies. *See, e.g.*, EX1011, 133-34; EX1025, 1314.

As Petitioner's expert Dr. Klibanov testified previously, "dot[ting] all the Is and cross[ing] all the Ts" was impractical in the field of protein formulation. As a result, "shortcuts" were often implemented. EX2004, 146:19-147:10, 152:5-17.

III. THE '265 PATENT

A. The Challenged Claims

The '265 patent claims liquid aqueous pharmaceutical formulations comprising a particular anti-IL-23p19 antibody having defined amino acid sequences for both its light (SEQ ID NO: 174) and heavy (SEQ ID NO: 176) chains. This specific antibody, referred to as "Antibody A" in the patent, has the same amino acid sequences as the antibody today known as risankizumab. *Compare* EX1001, SEQ ID NOs: 174 and 176, *with* EX2005, 1.

The claimed formulations also include a detergent, a tonicity agent, and optionally a buffer, have a pH within a narrow range (5.5 to 6.5 or narrower), and must be both stable and isotonic. Independent claim 19 is representative:

> 19. A liquid aqueous pharmaceutical formulation comprising
> (a) an anti-IL23p19 antibody, (b) a detergent, and (c) a tonicity agent,
> wherein the anti-IL23p19 antibody comprises a light chain amino acid sequence shown as SEQ ID NO: 174 and a heavy chain amino acid sequence shown as SEQ ID NO: 176,
> wherein the formulation is stable, isotonic, has a pH in the range of 5.5 to 6.5, and
> wherein the formulation optionally comprises a buffer.

Independent claim 7 is similar but requires a risankizumab concentration of 90 mg/ml. The challenged dependent claims additionally require that:

- the detergent is polysorbate 20 (PS20) (claims 8 and 20) and is present at a concentration of 0.2 mg/ml (claims 9 and 21);
- the formulation comprises a buffer (claims 10 and 22);
- the formulation is stable following storage for 8 weeks at 40° C (claim 14); and
- the formulation has an osmolality of 300 +/- 30 mOsmol/kg (claims 15 and 27) or a pH in the range of 5.5 to 6.1 (claims 16 and 28).[3]

B. The Specification

The specification describes the light and heavy chain sequences of risankizumab (SEQ ID Nos: 174 and 176). EX1001, 22:3-8. It also includes extensive characterization of that antibody, including affinity and kinetic data, selectivity data, pharmacokinetic data, and biophysical data. *Id.*, 85:32-92:21.

[3] Dr. Klibanov states that the claims and specification should recite "osmolality" instead of "osmolarity." EX1002 ¶ 264 n.10. He acknowledges that the units for osmolality are "mOsmol/kg," as recited in the claims. *Id*. Osmolality was also referenced during prosecution. EX1004, 7380.

The specification describes multiple exemplary risankizumab formulations using a diverse range of excipient categories and specific excipients within each category. *Id*., 90:52-55, 92:29-41, 92:56-93:8, 93:26-36; *see also id.*, 83:10-84:26. Each tested formulation was stable under the various disclosed conditions. *Id*., 90:48-55, cols. 91-92 (Table 18), 94:14-35.

Example 9, titled "Expression in NSO Cells and Biophysical Data," reports a formulation of up to 100 mg/ml risankizumab containing 115 mM NaCl (an ionic tonicity agent) and 20 mM sodium citrate (a buffer) at pH 6.0. *Id*., 89:62-90:55. The patent states that this formulation was stable at 4° C for at least 4 months. *Id.*, 90:52-55, cols. 91-92 (Table 18).

Example 11, titled "Pharmaceutical Compositions," describes three risankizumab formulations, labeled as Formulations 1-3. *Id.*, 92:22-94:12. Formulation 1 contains 10 mg/ml risankizumab, 125 mM NaCl (an ionic tonicity agent), 25 mM succinate (a buffer), and 0.2 mg/ml PS20 (a detergent), and has a pH typically in the range of 6.0 to 7.0, for example pH 6.5. *Id.*, 92:29-44. The patent reports that the osmolality of Formulation 1 is 300 +/- 30 mOsmol/kg and that the formulation is "particularly suitable for intravenous administration." *Id*., 92:44-55.

Formulation 2 contains 90 mg/ml risankizumab, 225 mM sorbitol (a nonionic tonicity agent), 4.4 mM succinate (a buffer), and 0.2 mg/ml PS20 (a detergent), and has a pH typically in the range of 5.5 to 6.5, for example pH 5.5 to 6.1. *Id.*, 92:56-

93:11. The patent reports that the osmolality of Formulation 2 is 300 +/- 30 mOsmol/kg and the formulation is "particularly suitable for subcutaneous administration." *Id*., 93:11-25.

Formulation 3 contains 90 mg/ml risankizumab, 240 mM sorbitol (a nonionic tonicity agent), no buffer, and 0.2 mg/ml PS20 (a detergent), and has a pH typically in the range of 5.5 to 6.5, for example pH 5.5 to 6.1. *Id.*, 93:26-94:2. The patent reports that the osmolality of Formulation 3 is 300 +/- 30 mOsmol/kg and the formulation is "particularly suitable for subcutaneous administration." *Id*., 94:2-12.

Example 12, titled "Stability of Pharmaceutical Compositions," reports stability testing of Formulations 2 and 3 after storage in a syringe at 40° C for 8 weeks, assessed by turbidity and percent monomer content. *Id.*, 94:14-35. Both formulations (Formulations 2 and 3) were stable under the tested conditions. *See id*. A summary of the formulations disclosed in these Examples is included below (Table 1).

	F1	F2	F3	Ex. 9
Ab Conc.	10 mg/ml	90 mg/ml	90 mg/ml	100 mg/ml
Buffer	Succinate (25 mM)	Succinate (4.4 mM)	None	Citrate (20 mM)
Tonicity Agent	NaCl (125 mM)	Sorbitol (225 mM)	Sorbitol (240 mM)	NaCl (115 mM)
Detergent	PS20 (0.2 mg/ml)	PS20 (0.2 mg/ml)	PS20 (0.2 mg/ml)	None
pH	6.0-7.0 (6.5)	5.5-6.5 (5.8)	5.5-6.5 (5.8)	6.0
Stable After		8 weeks at 40° C	8 weeks at 40° C	4 months at 4° C

Table 1. Summary of the formulations disclosed in Examples 9, 11, and 12 of the '265 patent

C. The Relevant Prosecution History

The '265 patent was filed as U.S. Application No. 13/870,061 on April 25, 2013, claiming priority to U.S. Provisional Patent Application No. 61/642,032, filed on May 3, 2012. EX1004, 1-7, 236. Patent Owner submitted an amended claim set on March 16, 2020, including new claims 37 and 49 (corresponding to issued claims 7 and 19 of the '265 patent, respectively). *Id.*, 7251-57.

On April 30, 2020, the Office issued a Non-Final Office Action, rejecting the pending claims, including claim 37, as lacking adequate written description. *Id.*, 7280-94. The Office alleged that claim 37 "encompasses a genus of formulations

that have no correlation between their structure and function" while "the specification provides insufficient written description to support the genus of formulations, comprising any detergent, encompassed by the claim." *Id.*, 7285.

On July 30, 2020, Patent Owner filed a Response traversing the rejection. *Id.*, 7373-83. The Response stated: "the present specification teaches all of the necessary components for preparing the claimed formulations and teaches how to combine the components to achieve the desired results." *Id.*, 7382. The Response also summarized "the information from Examples 9, 11, and 12 of the specification, which show that the claimed pH, osmolality, and stability can be achieved using the recited components, and this unequivocally shows that Applicant was in possession of the claim[ed] pharmaceutical compositions." *Id.*, 7380 (submitting a table summarizing the disclosed formulations).

The Response also discussed *Fresenius Kabi USA, LLC v. Coherus Biosciences, Inc.*, PGR2019-00064, involving written description and enablement challenges to U.S. Patent No. 10,155,039. *Id.*, 7379. Patent Owner explained that in *Fresenius*, the PTAB held that "a similar claim with only one exemplified embodiment in the specification possessed sufficient written description, even though the claim arguably encompassed 'millions of possible species.'" *Id.* Patent Owner submitted the *Fresenius* decision denying institution and reproduced an exemplary claim from the challenged patent. *Id.*, 7379, 7384-403.

On November 13, 2020, the Office issued a Final Office Action maintaining the written description rejection. *Id.*, 7621-40. In response to Patent Owner's reliance on *Fresenius*, the Examiner stated that interpretation of the term "stable" was at issue in *Fresenius*, whereas she was "not construing the term 'stable' to encompass a broader scope and is not imparting additional stability requirements on the claimed compositions." *Id.*, 7637.

On January 22, 2021, Patent Owner conducted an interview with the Examiner, who thereafter prepared an Applicant-Initiated Interview Summary. *Id.*, 7655-56. In the Summary, the Examiner stated that the issues discussed included "the 112(a) rejection over claims 37 and 49" and that "[t]he Attorney explained the relevancy of PGR-2019-00064 to the instant case." *Id.* The Examiner further discussed potential claim amendments. *Id*.

Patent Owner subsequently filed an Amendment and Response on February 12, 2021 (*id*., 7659-70), which stated that it was "consistent with the discussion during the interview," and traversed the written description rejection. *Id.*, 7665. The claims were amended to require a tonicity agent and optionally a buffer. *Id.*, 7661-62. Patent Owner also explained how the exemplary formulations in the specification provide adequate support for the amended claims. *Id.*, 7666-69.

The claims were thereafter allowed. *Id.*, 7678-85. The Examiner explained that "the specification demonstrates that the anti-IL-23p19 antibody recited in the

claims is self-buffering and can be formulated with different tonicity agents, while maintaining its stability properties." *Id.*, 7684.

IV. PETITIONER HAS NOT ESTABLISHED THAT IT IS MORE LIKELY THAN NOT THAT ANY CHALLENGED CLAIM IS UNPATENTABLE

A. Petitioner's Failure to Properly Construe "Stable" Renders the Petition Deficient Under 37 C.F.R. § 42.204(b)(3)-(4)

For each challenged claim, the petition must set forth both "[h]ow the challenged claim is to be construed" and "[h]ow the construed claim is unpatentable under the statutory grounds identified." 37 C.F.R. § 42.204(b)(3)-(4). As set forth below, the Petition does not meet these requirements and should be denied.

Petitioner's written description and enablement grounds are premised entirely upon the assertion that the claims recite a genus of formulations defined by a "functional" claim term: "wherein the formulation is stable." *E.g.*, Pet. at 50 (asserting that "functionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support") (citations omitted); *id.* at 71 (asserting that "use of broad functional claim limitations raises the bar for enablement") (citations omitted). According to Petitioner, it is this "stable" functionality that, combined with alleged unpredictability in the art, renders the claimed genus inadequately described and non-enabled. Pet. at 1 ("The challenged claims recite this genus in classically functional terms—not based on what the antibody formulation is, but based on whether it is 'stable.'").

Despite the criticality of the "stable" limitation to Petitioner's grounds, Petitioner ***does not construe the term***. Under the alleged rubric of claim construction, Petitioner instead argues that the claims must "encompass" formulations that are (1) "stable following storage in a syringe for 8 weeks at 40° C" and (2) "stable following storage at 4° C for at least 4 months." Pet. at 34-37. But this "construction" does not explain the ***meaning*** of the term "stable." It merely imports, wrongly, ***storage conditions*** under which some formulations are "stable." *See infra* § IV.B. In other words, despite stability being fundamental to its challenges, Petitioner never explains how the claims, when properly construed, are unpatentable. This failure warrants denial under 37 C.F.R. § 42.204(b)(3) and (4). *See, e.g.*, *OrthoPediatrics Corp. v. K2M, Inc*., IPR2018-01548, Paper 9 at 9-11 (PTAB Mar. 1, 2019) (denying institution because "Petitioner's contentions [were] limited to how the claim limitations at issue *should not be construed*" and Petitioner therefore failed to meet the burden of explaining "how the *construed* claim is unpatentable"); *LG Display Co. v. Delaware Display Grp. LLC*, IPR2014-01359, Paper 12 at 5-7 (PTAB Mar. 2, 2015) (denying institution and finding that petitioner failed to meet the requirements of 37 C.F.R. § 42.204(b)(3)-(4)).

B. "Stable" Should Be Construed to Have Its Plain and Ordinary Meaning

"[T]he words of a claim are generally given their ordinary and customary meaning." *Phillips v. AWH Corp*., 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (citation omitted). "There are only two exceptions to this general rule: 1) when a patentee sets out a definition and acts as his own lexicographer, or 2) when the patentee disavows the full scope of a claim term either in the specification or during prosecution." *Thorner v. Sony Comput. Ent. Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). Petitioner does not argue that either exception applies here. *See* Pet. at 34 ("The '265 patent does not define the term 'stable.'"). Accordingly, the term "stable" should be given its ordinary and customary meaning as set forth below.

Petitioner's "construction" is improper because it departs from the ordinary and customary meaning and instead reads in certain storage conditions from (i) an example in the specification and (ii) from dependent claim 14. Specifically, Petitioner contends that "wherein the formulation is stable" should encompass formulations that are "stable following storage at 4° C for at least 4 months," as described in Example 9. Pet. at 36-37. A POSA would have appreciated that the storage conditions described Example 9 are exemplary only and would not have

understood the term "stable" to require those conditions.[4] *See, e.g.*, EX1002 ¶ 100 (Dr. Klibanov identifying various types of "accelerated stability tests"); *see, e.g.*, *SuperGuide Corp. v. DirecTV Enters., Inc*., 358 F.3d 870, 875 (Fed. Cir. 2004) ("[A] particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment."). Petitioner also contends that "wherein the formulation is stable" should be construed to encompass formulations that are "stable following storage in a syringe for 8 weeks at 40° C," as recited in dependent claim 14. Pet. at 34-35. The doctrine of claim differentiation confirms that "stable" is not so limited. *Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1326 (Fed. Cir. 2008) (declining to construe "capillary" as requiring uniformity where a dependent claim expressly recited capillary uniformity, stating that "the structure of the claims confirms that uniformity was not intended to be a feature of the invention as a whole"). The Board should therefore reject Petitioner's "construction."

Consistent with the intrinsic evidence, the term "stable" should instead be given its plain and ordinary meaning, which requires that the formulation maintain

[4] Petitioner states that Example 9 is not within the scope of the challenged claims, yet nevertheless attempts to import the storage conditions from Example 9 into the claims. *Compare* Pet. at 27, *with id.* at 36-37.

stability suitable for its pharmaceutical application. *Phillips*, 415 F.3d at 1312 ("the words of a claim are generally given their ordinary and customary meaning"). *First*, nothing in independent claims 7 or 19 associates "stable" with any specific storage conditions. Indeed, under the doctrine of claim differentiation, dependent claim 14, which recites that "the formulation is stable following storage in a syringe for 8 weeks at 40° C," confirms that "stable" is not so limited. *Praxair*, 543 F.3d at 1326.

Second, the patent emphasizes that the formulations of the present invention are suitable for pharmaceutical application. *See* EX1001, 2:6-9 ("A particular aim of the present invention is to provide pharmaceutical compositions for antibody molecules with favorable stability and storability."), 84:21-26 ("In one aspect, the pharmaceutical compositions disclosed herein are physico-chemically stable"); *see also id*., 92:29-46, 92:56-93:13, 93:25-94:4 (describing exemplary formulations that are "particularly suitable" for intravenous and subcutaneous administration). Contrary to Petitioner's argument, the specification provides examples showing various storage conditions and lengths of time under which the formulations may be stable, various measures and degrees of stability, and various methods for evaluating stability. Example 9, for instance, measures "[s]tability" using analytical ultracentrifugation ("AUC") and size exclusion chromatography ("SEC") at 1 and 4 months at 4° C. *Id.*, cols. 91-92 (Table 18). Example 12 discloses the "[s]torage [s]tability" of Formulations 2 and 3, which are described as "particularly suitable for

subcutaneous administration," and provides measurements of pH, osmolality, turbidity (measured by nephelometry), and percent monomer (measured by high-performance SEC) initially and after 8 weeks in storage at 40° C. *Id.*, 93:11-13, 94:2-4, 94:20-21, 94:26-36. The specification thus confirms that "stable" should be given its plain and ordinary meaning.

Third, the Examiner likewise understood the term "stable" in a manner consistent with the common usage in the art. *E.g.*, EX1004, 7624 ("The specification teaches that the compositions of the invention are physico-chemically stable."). Indeed, the Examiner explained that she was ***not*** incorporating specific heightened requirements, such as "stability . . . over different periods of time," into the term "stable." *Id.*, 7637 ("In the instant case, the Examiner is not construing the term 'stable' to encompass a broader scope and is not imparting additional stability requirements on the claimed compositions."). Accordingly, the prosecution history also confirms that the plain and ordinary meaning of the "stable" does not require stability under any specific storage conditions.

The extrinsic evidence also supports that "stable" should be given its plain and ordinary meaning. The term "stable" is commonly used in the context of protein pharmaceutical formulations. *See, e.g.*, EX1011, Title; EX1012, 299 ("Several recent reviews discuss the importance of protein stability in formulation development . . . ."); EX1013, Title ("Stability of Protein Pharmaceuticals: An

Update"). Various methods for evaluating the stability of protein pharmaceutical formulations—including those described in the specification—were known in the art. *See, e.g.*, EX1001, Exs. 9, 12; EX1002 ¶ 100. Accordingly, a POSA would have readily understood the term "stable" and how to assess whether a given formulation is "stable" as required by the claims. Indeed, Petitioner's expert Dr. Klibanov has previously stated as follows:

> "Stable" is a common term in chemistry and pharmaceutical formulations that is given meaning by the context in which it is used. . . . A POSA would understand that any or all of these various categories of parameters may be relevant and important based on the circumstances. Furthermore, (s)he would recognize which specific categories of stability should be considered for a given scenario.

EX2006 ¶ 95.

Petitioner acknowledges that there is no contrary definition of "stable" in the '265 patent specification. Pet. at 34. In the absence of a clear intent to define the term "stable" in a manner different from the common usage in the art, the Board and courts have deemed the term to have its plain and ordinary meaning. *See, e.g.*, *Fresenius*, PGR2019-00064, Paper 10 at 7-10; *Silvergate Pharms. Inc. v. Bionpharma Inc.*, No. 16-cv-876, 2018 WL 1610513, at *10 (D. Del. Apr. 3, 2018) (applying the plain and ordinary meaning of "stable").

Accordingly, the term "stable" should be given its plain and ordinary meaning, which requires that the formulation maintain stability suitable for its pharmaceutical application.[5]

C. Ground 1: Petitioner Fails to Satisfy Its Burden of Demonstrating that Any Challenged Claim Lacks Written Description Support

The written description requirement is met when the specification "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). "[T]he hallmark of written description is disclosure," which must be read "from the perspective of a [POSA]." *Id*. For genus claims, the written description requirement is satisfied when the specification discloses a representative number of species falling within the scope of the genus or structural features common to the members of the genus such that a POSA can visualize or recognize the members of the genus. *Id.* at 1350.

Petitioner's written description analysis is premised on its allegation that the claims are too broad, the specification too narrow, and the art too unpredictable to bridge the gap. *See* Pet. at 51-62. As explained below, each aspect of Petitioner's analysis is flawed.

[5] For purposes of this Preliminary Response, Patent Owner does not dispute that the preambles of claims 7 and 19 are limiting.

1. Claims 7 and 19

a. Petitioner Mischaracterizes the Scope of the Claims

Petitioner contends that the challenged claims lack adequate written description because they "encompass a broad genus of antibody formulations, recited in generic and functional terms," allegedly covering "millions of potential formulations." Pet. at 51-53. Petitioner is wrong on both the facts and the law.

As an initial matter, multiple ***structural elements*** define the claimed formulations. This includes a specific antibody, risankizumab, defined by its complete heavy and light chain amino acid sequences. EX1001, claims 7, 19. The claims further recite a group of well-known excipients that impart isotonicity and stability and a narrow pH range. *Id.*; EX1002 ¶¶ 39 (Dr. Klibanov: detergents "were known to be one of the main excipients often used in antibody formulations"), 48 (buffers "have been routinely utilized in protein drug products for pH control"), 57 (tonicity agents "include polyols, salts, and amino acids"). Petitioner's arguments, which ignore these structural elements, contravene the Federal Circuit's guidance that such elements must be considered in evaluating written description. *See Ariad*, 598 F.3d at 1350 (the written description requirement is met by the disclosure of "a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials").

The "classes of excipients generally" recited in the claims (Pet. at 51-52) are adequately supported because, as Petitioner acknowledges, they were well-known in the art. *See Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.*, 276 F. Supp. 3d 629, 648 (E.D. Tex. 2016), *aff'd*, 739 F. App'x 643 (Fed. Cir. 2018) ("when a genus is well understood in the art and not itself the invention but is instead a component of the claim, background knowledge may provide the necessary support for the claim"). Judge Bryson's illustration in *UroPep* is instructive:

> [A] claim might be directed to the novel use of a particular salt, where the salt must be dissolved in a "solubilizing agent." The broad genus of "solubilizing agents" would not require representative species if persons of skill knew of many solvents that could dissolve the salt, and thereby serve as a "solubilizing agent" in that invention. Patents in the chemical field may often involve claims that include well-understood genera.

Id. at 649; *see also Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006) ("the forced recitation of known [compounds] in patent disclosures would only add unnecessary bulk to the specification").

Petitioner's attempt to enumerate the "broad" genus based on Dr. Klibanov's calculation disregards the claimed invention as a whole. Pet. at 52-53 (citing EX1002 ¶¶ 181-182, 220-221, App'x B). For example, in identifying potential excipients for his calculations, Dr. Klibanov looked generally at "injectable"

formulations, including small molecules and other unrelated compounds, ***rather than aqueous formulations of antibodies***. EX1002, App'x B (citing EX1015, EX1042); *see* EX1015, Abstract ("a current survey of excipients used in approved injectable products"); EX1042, 292 ("formulations of approved protein drugs"); *see also* EX1002 ¶¶ 47, 51, 62 (identifying detergents, buffers, and tonicity agents used in "injectable products"). Similarly, he includes excipients used in lyophilized formulations, even though the claims are directed to ***aqueous*** antibody formulations. EX1002, App'x B; *see* EX1042, 292 ("the composition of liquid and lyophilized protein formulations"); *id.*, 296, 299. Petitioner does not even argue that many of these excipients would have been understood as suitable for the claimed invention—by way of example, many had never been used in any commercial liquid antibody formulation. For instance, while Dr. Klibanov identifies eleven detergents, ***only two*** had been used in commercial liquid antibody formulations known as of 2012 (one of which, polysorbate 20, is tested in the '265 patent). *See infra* App'x A. Similarly, while Dr. Klibanov identifies twenty-seven tonicity agents, ***only eight*** had been used in commercial antibody formulations (two of which, sorbitol and NaCl, are tested in the '265 patent). *Id.*

Similarly, Dr. Klibanov assumes that a POSA would need to test at least 10 or 15 exemplary concentrations for each excipient. Pet. at 52-53; EX1002 ¶¶ 181-182. But Petitioner provides no basis for this assumption, and by way of example,

the approved commercial antibodies with "liquid aqueous pharmaceutical" formulations use narrow ranges of the claimed excipients. *See infra* App'x A. Dr. Klibanov also disregards the claim limitation "isotonic," which limits the concentration of the claimed tonicity agent to a relatively narrow range. *See, e.g.*, EX1042, 299 ("In order to maintain isotonicity in a parenteral formulation, salt concentrations are generally limited . . . .").

Dr. Klibanov also argues that each of these excipients and concentrations must be tested in a combinatorial manner, amounting to "millions of potential formulations." Pet. at 52-53; EX1002 ¶¶ 181-82. But Dr. Klibanov has previously testified to the contrary. *See* EX2004, 146:19-147:10 (testifying that in the field of protein formulation, it is "very typical" to "cut some corners" based on "educated guesses" and "scientific judgments"); *id*., 152:5-17 (Dr. Klibanov testifying that without taking "some shortcuts," "you will never complete the formulation development"); *see also* EX2003, 1953 (Table I) (describing fractional factorial design that allowed researchers to evaluate seven variables using only eight formulations). Unsurprisingly, courts have rejected similar numerosity arguments that do not reflect the perspective of a POSA and overstate the scope of the claims. *See, e.g.*, *Allergan Sales, LLC v. Sandoz, Inc*., 717 F.App'x 991, 995-96 (Fed. Cir. 2017) (rejecting Sandoz's numerosity arguments, which overstated the number of drug forms that a POSA would need to make and test); *Warner Lambert Co. v. Teva*

Pharms. USA, Inc., No. 99-cv-922, 2007 WL 4233015, at *13 (D.N.J. Nov. 29, 2007) (crediting an expert's opinion that a POSA "would set up a fractional factorial design, allowing the effect of multiple formulation variables . . . to be analyzed simultaneously with a limited set of routine experiments run simultaneously").

Petitioner's arguments, which ignore the claimed invention as a whole, do not demonstrate a lack of written description of claims 7 and 19.

b. Petitioner's Evidence of Unpredictability Is Not Directed to the Claimed Invention

Petitioner's repeated reliance on the "unpredictability in the art" (*e.g*., Pet. at 54-57, 60, 62) is misplaced because it does not account for "the predictability of ***the aspect at issue***." *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005). Indeed, much of Petitioner's underlying evidence focuses on general unpredictability stemming from ***differences among antibodies or even other proteins*** (i.e., antibodies or proteins having different amino acid sequences, which in turn results in unpredictability when a formulation for one antibody is repurposed for a different antibody). *See, e.g.*, Pet. at 5 (asserting unpredictability due to the "unique" behavior of each antibody); *id*. at 5-6 (discussing the "diversity" of antibodies and "their individual interplay with excipients"); *id*. at 13 ("protein specific"); *see also* EX1014, 14 ("It should be stressed that one formulation excipient stabilizing a

specific antibody may not be suitable for another because of the differences in their sequence.").

Even when Petitioner's references discuss stability effects of excipients in an antibody-agnostic manner, they explain that these excipients, in some cases, could increase or decrease the stability of formulations—not that they are incompatible with, or would render unstable, antibodies generally or risankizumab specifically. *See, e.g.*, EX1014, 16 ("A variety of formulation excipients have been shown to stabilize antibodies under different processing conditions and during storage, including sugars, polyols, amino acids, surfactants, and polymers.").

The general unpredictability espoused by Petitioner does not bear on the adequacy of the written description of the challenged claims, which are limited to formulations of one specific antibody, risankizumab. Here, every formulation tested in the '265 patent is stable. *See supra* § III.B. Indeed, despite having the burden of proof, Petitioner has not identified ***any*** formulation of risankizumab that is not stable. Petitioner fails to cite even a single prior art reference mentioning risankizumab. In the absence of such evidence, Petitioner fails to reasonably establish the unpredictability of "the aspect at issue," i.e., that a POSA, based on the disclosures of the '265 patent, would not have believed that stability would be maintained with other risankizumab formulations covered by the challenged claims. *See Bilstad v. Wakalopulos*, 386 F.3d 1116, 1125 (Fed. Cir. 2004) (the

unpredictability assessment focuses on whether "the difference between members of the group is such that the person skilled in the art would not readily discern that other members of the genus would perform similarly to the disclosed members").

Petitioner's cherry-picked statements from U.S. and European prosecution (*see* Pet. at 54-55) are irrelevant to written description. The statements relied on by Petitioner reflect general unpredictability in the art relevant to obviousness, which is analyzed ***without*** the disclosures of the '265 patent. But "[w]hat the specification at issue ***describes*** to a relevant artisan . . . presents a distinct question from what a relevant artisan would have found obvious from the prior art without the specification." *BASF Plant Sci., LP v. Commonwealth Sci. & Indus. Rsch. Org.*, 28 F.4th 1247, 1265 n.4 (Fed. Cir. 2022).

In sum, Petitioner has failed to demonstrate any unpredictability applicable to the claimed invention. Petitioner's arguments based on generalized unpredictability do not demonstrate lack of written description.

c. Petitioner's Evaluation Improperly Discounts the Description Provided in the Specification

Petitioner next argues that the challenged claims are not adequately described because the '265 patent allegedly does not disclose a representative number of formulations or a structural feature that correlates with stability. Pet. at 53-62. Petitioner's arguments again lack merit.

Representative Number of Species: The risankizumab formulations disclosed in the '265 patent comprise a variety of representative excipients from each claimed excipient category. For instance, Formulations 1-3 contain polysorbate 20, a representative detergent. *Supra* § III.B; *see* EX1002 ¶ 76 ("the detergents polysorbates 20 and 80, among others, were commonly used in protein formulations"). Formulations 1-3 each contain NaCl or sorbitol, which respectively represent ionic and nonionic tonicity agents. *Supra* § III.B; *see* EX1002 ¶ 57 (tonicity agents "include salts, polyols, and amino acids"). Formulations 1-3 contain succinate buffer or no buffer, representing formulations with and without buffer. *Supra* § III.B; *see* EX1002 ¶ 48 (buffers "have been routinely utilized in protein drug products for pH control"); *id*. ¶ 53 ("Antibodies formulated at high protein concentrations were also known in the pre-2013 art as having the potential for self-buffering."). Formulation 1 is reported to be "particularly suitable for intravenous injection." EX1001, 92:45-46. Formulations 2-3 are reported to be "particularly suitable for subcutaneous injection," and further were empirically shown to be stable following eight weeks in storage at 40° C. *Id*., 93:11-13, 94:2-4, Ex. 12. Tellingly, Petitioner fails to identify ***any*** risankizumab formulation that meets the multiple structural limitations of the claims but is unstable.

Petitioner argues that "the FDA had yet to approve a buffer-less antibody formulation." Pet. at 55-56. This is irrelevant to the representativeness of the

disclosed formulations. The '265 patent discloses that a risankizumab formulation without buffer is stable and even remains stable in a syringe, at an elevated temperature, for eight weeks. *See* EX1001, Ex. 12. Combined with the general knowledge in the art, a POSA would have understood that buffer could be omitted from higher concentration formulations of risankizumab, but that buffer may be necessary at lower concentrations. *See, e.g.*, EX1018, 491 ("For highly concentrated protein solutions the buffer capacity by the proteins becomes equipotent to conventional buffer excipients and can replace the latter in terms of pH stabilization.").

Petitioner also focuses on the absolute number of representative formulations disclosed in the '265 patent. *See* Pet. at 53-58. But this is not determinative, and courts and the Board have found similar claims adequately supported by even a single formulation. In *Fresenius*, discussed during prosecution, the Board denied institution of written description and enablement challenges. PGR2019-00064, Paper 10 at 11-18; *supra* § II.C. Similar to the challenged claims here, the claims in *Fresenius* were directed to a "stable" aqueous pharmaceutical formulation comprising (1) a specific antibody defined by its amino acid sequences (adalimumab), (2) a limited group of specific excipient categories, and (3) a narrow pH range. PGR2019-00064, Paper 10 at 4. Like Petitioner, which alleges the challenged claims encompass "millions of potential formulations" (Pet. at 46), the

petitioner in *Fresenius* alleged that the claims encompassed "millions of possible [formulations]." PGR2019-00064, Paper 10 at 12. Although the *Fresenius* specification disclosed only a ***single formulation*** within the scope of those claims, the Board rejected the petitioner's representative species arguments, as the specification identified with sufficient clarity each of the ingredients that must be included (i.e., a buffer, a sugar, etc.). *Id.* at 13-14; *see also infra* § V.B.1.

In *Helsinn Healthcare S.A. v. Dr. Reddy's Laboratories, Ltd.*, the court similarly upheld claims directed to "stable" aqueous formulations comprising a small molecule pharmaceutical, a tonicifying agent, and a chelating agent. No. 12-cv-2867, 2017 WL 631899, at *25-31 (D.N.J. Feb. 14, 2017). The specification again disclosed only a single formulation within the scope of the claims—fewer than the number of stable formulations disclosed in the '265 patent. *Id*. Notwithstanding defendant's assertion that the claims encompassed vast numbers of possible formulations, the court found adequate written description because the specification "disclose[d] each component of the formulations set forth in the asserted claims" and included an exemplary formulation shown to be stable. *Id*.; *see also Bilstad*, 386 F.3d at 1123-25 (collecting cases where a single representative embodiment was sufficient to support written description of a claimed genus).

In *Alcon Research Ltd. v. Barr Laboratories, Inc.*, the patent challenger argued that the claims lacked adequate written description support. 745 F.3d 1180,

1190 (Fed. Cir. 2014). According to the challenger, the claims encompassed "a method for enhancing the chemical stability of ***innumerable*** prostaglandins by adding to them PECO [polyethoxylated castor oil] in an endless number of combinations and concentrations," while the specification disclosed data from just "one compound." *Id*. The Federal Circuit held otherwise, explaining that the patent "provides exemplary formulations that embody the claimed invention," "discloses data generated by the inventor from accelerated stability testing," and "describes various types of PECOs" and "various formulation parameters, including osmolality and pH, that may be selected when practicing the invention." *Id.* at 1191-92.

Common Structural Feature: The challenged claims identify a particular structure—i.e., the novel and nonobvious combination of risankizumab, a detergent, and a tonicity agent, with or without buffer, in a narrow range of pH—that achieves stability and isotonicity. This correlation is supported by stability and osmolality testing in the specification. *E.g.*, EX1001, Ex. 12.

Instead of considering the specific, claimed structural elements collectively, Petitioner focuses on general unpredictability associated with each separate claim element. *See* Pet. at 59-60. For the reasons discussed above, this generalized unpredictability is insufficient to support Petitioner's arguments. *Supra* § IV.C.1.b. While Petitioner speculates that the claimed combination of structural elements

"would not remove [the] unpredictability" (Pet. at 60-61), Petitioner does not identify any formulation containing the claimed structural elements that is ***not*** stable.

Petitioner attempts to distinguish *Fresenius*, arguing that the *Fresenius* patent limited the variety of suitable excipients based on three lists of excipients in the specification. Pet. at 58-59; *see also id*. at 40-41. But these lists are not claim limitations—and therefore cannot serve as structural features common to the claimed genus. *Electro Med. Sys. v. Cooper Life Sci., Inc*., 34 F.3d 1048, 1054 (Fed. Cir. 1994) ("claims are not to be interpreted by adding limitations appearing only in the specification"). Notably, contrary to Petitioner's assertion (Pet. at 41), the Board in *Fresenius* did not credit these lists in denying institution and rejecting petitioner's common structural features argument. *Fresenius*, PGR2019-00064, Paper 10 at 12-15.

d. Petitioner's Cases Are Inapposite

Petitioner's written description arguments rest on cases involving claims that are fundamentally different from those challenged here. *AbbVie Deutschland GmbH v. Janssen Biotech, Inc*., the principal written description case relied on by Petitioner (*see* Pet. at 50, 54, 55, 58), was not a formulation case. 759 F.3d 1285 (Fed. Cir. 2014). Instead, it involved claims to antibodies defined solely by their binding characteristics rather than by specific amino acid sequences. *Id.* at 1292, 1297-302. Further, the evidence showed that the disclosed antibodies did not represent other

antibodies encompassed by the claims, that no structure-function correlation was established, and that there was no predictable way to arrive at other claimed antibodies from the disclosed antibodies. *Id*. at 1300-01. In contrast, the claims here recite the complete amino acid sequences of the light and heavy chains, as well as additional well-known categories of excipients and a narrow pH range—and Petitioner has adduced no evidence that the described formulations are not representative or lack common structural features. *See Rockwool Int'l A/S v. Knaupf Insulation, Inc*, PGR2022-00022, Paper 10, at 14, 16-17 (PTAB July 6, 2022) (denying institution due to the petitioner's failure to show lack of written description because "the common structural feature is actually recited in the claim").

Amgen Inc. v. Sanofi, another case relied on by Petitioner (Pet. at 50), is also inapposite. 872 F.3d 1367 (Fed. Cir. 2017). In *Amgen*, the claims broadly covered "the entire genus of antibodies that bind to specific amino acids" in a particular protein, rather than any specific antibody defined by its amino acid sequence. *Id.* at 1372. The Federal Circuit rejected the patentee's attempt to claim the antibody by defining amino acids in its target, explaining that this "contradicts the statutory 'quid pro quo' of the patent system where 'one describes an invention, and, if the law's other requirements are met, one obtains a patent.'" *Id.* at 1378-79. Here, in contrast, the challenged claims are tailored to the inventors' novel and nonobvious discovery that a specific antibody, risankizumab, can be stably formulated using select

categories of excipients in a narrow pH range. The specification discloses multiple exemplary formulations and empirical stability data, and the claims conform to the disclosures—the statutory quid pro quo of the patent system is satisfied.

In sum, Petitioner's written description analysis is flawed because it fails to consider the claimed invention as a whole; argues unpredictability without accounting for the claimed invention; improperly discounts the teachings of the specification; and disregards relevant authority. As such, Petitioner fails to satisfy its burden of demonstrating that claims 7 and 19 lack written description support.

2. Other Challenged Claims

Petitioner does not introduce any new or different arguments with respect to the challenged dependent claims. As with claims 7 and 19, Petitioner's written description analysis fails to address the unpredictability of the "aspect at issue" (liquid, aqueous, risankizumab formulations); ignores the nature of the invention and the perspective of the POSA in calculating the number of formulations potentially encompassed by the claims; and improperly discounts the representative examples provided in the specification. *See* Pet. at 62-70.

Claims 8, 9, 20, and 21: Claims 8 and 20 depend from claims 7 and 19, respectively, and limit the claimed detergent to polysorbate 20, a well-known detergent used in numerous antibody formulations as of 2012. EX1002 ¶ 76; *see infra* App'x A. Claims 9 and 21 depend from claims 8 and 20 and further limit the

concentration of polysorbate 20 to 0.2 mg/ml. Polysorbate 20 is tested in multiple formulations disclosed in the specification at this concentration. *E.g.,* EX1001, Exs. 11, 12.

Petitioner fails to demonstrate lack of adequate written description of these claims for at least the reasons set forth above. Petitioner's calculations of the number of formulations potentially within the scope of these claims include, for example, numerous excipients used with small molecules or lyophilized formulations, and Petitioner fails to introduce evidence that any risankizumab formulation meeting the structural limitations of the claims is not stable. Pet. at 64-67.

Claims 10 and 22: Claims 10 and 22 depend from claims 7 and 19, respectively, and require the presence of buffer. The specification discloses multiple formulations that contain buffer. *E.g.*, EX1001, Exs. 9, 11, 12. Petitioner concedes that buffers were a well-known class of excipients for liquid aqueous formulations of antibodies, and that one of the stable Example 11 formulations falls within the scope of these claims. *See* Pet. at 68; EX1002 ¶ 48.

Petitioner fails to demonstrate lack of adequate written description of these claims for at least the reasons set forth above. Petitioner's calculations of the number of formulations potentially within the scope of these claims include, for example, numerous excipients used with small molecules or lyophilized formulations, and

Petitioner fails to introduce evidence that any risankizumab formulation meeting the structural limitations of these claims is not stable. *See* Pet. at 67-68.

Claim 14: Claim 14 depends from claim 7 and recites that "the formulation is stable following storage in a syringe for 8 weeks at 40° C." EX1001, claim 14. Petitioner acknowledges that these storage conditions were applied in Example 12 of the '265 patent, and that Formulations 2 and 3 were reported as stable under these conditions. *Id*., Ex. 12; *see* Pet. at 63.

Petitioner fails to demonstrate lack of adequate written description of this claim for at least the reasons set forth above. Petitioner fails to introduce evidence that any risankizumab formulation meeting the structural limitations of claim 14 is not stable following storage in the disclosed conditions. Further, Petitioner's calculations of the number of formulations potentially within the scope of claim 14 include, for example, numerous excipients used with small molecules or lyophilized formulations. *See* Pet. at 62-64.

Claims 15, 16, 27, and 28: Claims 15 and 27 depend from claims 7 and 19, respectively, and further recite that the claimed formulations have an osmolality of 300 +/- 30 mOsmol/kg. Claims 16 and 28 also depend from claims 7 and 19, respectively, and further narrow the pH range to 5.5 to 6.1. Petitioner concedes that the stable Example 11 formulations fall within the scope of these claims. *See id.* at 69, 70.

Petitioner fails to demonstrate lack of adequate written description of these claims for the reasons set forth above. Petitioner's calculations of the number of formulations potentially within the scope of these claims include, for example, numerous excipients used with small molecules or lyophilized formulations, and Petitioner fails to introduce evidence that any risankizumab formulation meeting the structural limitations of these claims is not stable. *See id.* at 68-70.

For at least these reasons, Petitioner has not met its burden of demonstrating that it is more likely than not that the '265 patent does not adequately describe any challenged claim.

D. Ground 2: Petitioner Fails to Satisfy Its Burden of Demonstrating that Any Challenged Claim Is Not Enabled

To establish that a claim is non-enabled, a challenger must show that a POSA would not be able to practice the claimed invention without "undue experimentation." *Alcon*, 745 F.3d at 1188-89. A showing of "undue experimentation" requires the challenger to first put forward evidence that some experimentation is needed to practice the claimed invention. *Id.* After that threshold showing has been made, the *Wands* factors may then be considered to determine whether the amount of experimentation is "undue." *Id.*; *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

Here, Petitioner has not established that any experimentation would be needed to practice the claimed invention. Instead, Petitioner assumes some experimentation would be necessary and improperly applies the *Wands* factors "as if they were a generalized test for deciding whether a patent disclosure is sufficiently detailed to support a broad claim." *Alcon*, 745 F.3d at 1189. But even if Petitioner had made the threshold showing that some experimentation would be needed to practice the claimed invention, it has failed to demonstrate that such alleged experimentation would be undue.

1. Claims 7 and 19

a. Petitioner Fails to Demonstrate that Any Experimentation Is Necessary

The '265 patent claims are directed to the discovery that a specific antibody, risankizumab, can be combined with specific categories of excipients to achieve a stable liquid aqueous formulation. The specification provides examples of risankizumab stably formulated in a narrow pH range with a detergent, a tonicity agent, and optionally a buffer. *See* EX1001, Ex. 11 (disclosing Formulations 1-3). The specification also provides empirical evidence demonstrating that the resulting formulations are stable. *Id*., Ex. 12 (evaluating stability of Formulations 2 and 3).

Petitioner's enablement arguments are substantially the same as its written description arguments. Specifically, Petitioner contends that "the '265 patent sends the POSA on an iterative, trial-and-error quest of hypothesizing, formulating, and

testing a vast genus of formulations to *figure out* which formulations satisfy the functional claim limitations." Pet. at 71 (emphasis in original). But Petitioner's contention rests on sheer conjecture that a significant number of formulations otherwise within the scope of the challenged claims are not stable, necessitating the alleged trial-and-error quest. Critically, however, neither Petitioner nor Dr. Klibanov identified ***any*** formulation—let alone a significant number of formulations—that is not stable. *Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co.*, 308 F.3d 1167, 1186 (Fed. Cir. 2002) (finding "general and vague . . . statements" regarding inoperative species unpersuasive to support a claim of undue experimentation); *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 (Fed. Cir. 2020) ("Conducting the *Wands* analysis has routinely involved concrete identification of at least some embodiment or embodiments asserted not to be enabled."). Notably, ***all*** of the tested formulations were stable. EX1001, Ex. 12.

Because Petitioner has not made a threshold showing that some experimentation is necessary, its enablement arguments must fail. *Alcon*, 745 F.3d at 1189 (absent a "threshold showing that any experimentation is necessary," there is no basis for holding that claims are not enabled); *Atlas Powder Co. v. E.I. du Pont De Nemours & Co*., 750 F.2d 1569, 1577 (Fed. Cir. 1984) (upholding enablement of claims directed to an emulsion blasting agent comprising an emulsifying agent when the defendant failed to identify any emulsifiers that are inoperable).

b. Petitioner Fails to Demonstrate that Any Alleged Experimentation Required to Practice the Claimed Invention Would Be Undue

Even if Petitioner had established that some experimentation would be needed to practice the claimed invention (e.g., by identifying an inoperative embodiment(s), which it has not), it has not shown that such experimentation would be undue. In determining whether any alleged experimentation would be undue, the *Wands* factors may be considered and include the: (1) quantity of experimentation necessary; (2) amount of direction or guidance presented; (3) presence or absence of working examples; (4) nature of the invention; (5) state of the prior art; (6) relative skill of those in the art; (7) predictability or unpredictability of the art, and (8) breadth of the claims. *Wands*, 858 F.2d at 737. Not all of the factors must be considered or met in every case. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991) ("[I]t is not necessary that a court review all the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory."). Regardless, Petitioner's *Wands* factor analysis is flawed, and the cases it cites are inapposite.

i. Petitioner's Analysis of the *Wands* Factors Is Deficient

Petitioner's enablement arguments, like its written description arguments, overstate the breadth of the claims, understate the guidance in the specification, and rely on references unrelated to risankizumab or evidence of generalized

unpredictability instead of unpredictability of risankizumab formulations. As discussed below, these errors plague Petitioner's analysis of the *Wands* factors.

Wands Factors (4) & (8): Nature of the Invention and Breadth of the Claims: The '265 patent claims are narrowly tailored to risankizumab, a specific antibody, combined with particular categories of well-known monoclonal antibody excipients (a detergent, a tonicity agent, and optionally a buffer) at a pH within a narrow range (5.5 to 6.5) to achieve a stable, isotonic formulation suitable for pharmaceutical use.

Petitioner characterizes the nature of the invention as "[m]aking stable antibody formulations" and describes it as "complex and unpredictable." Pet. at 74. But the claims are not directed to stable formulations of ***any*** antibody; they are directed to stable formulations of ***risankizumab***, a specific antibody defined by specific amino acid sequences. Petitioner's cited references, which generally describe unpredictability stemming from differences among antibodies resulting from different amino acid sequences, are therefore inapplicable. *See supra* § IV.C.1.b; *Streck, Inc. v. Rsch. & Diagnostic Sys., Inc*., 665 F.3d 1269, 1291-92 (Fed. Cir. 2012) (testimony discussing "difficulties . . . ***before*** [the inventor] disclosed his invention" is immaterial to whether "undue experimentation would be necessary ***once*** the teachings in the patents-in-suit were known").

In characterizing the breadth of the claims, Petitioner also ignores the claimed structural elements and overstates their scope by, for example, relying on excipients

and concentration ranges that a POSA would appreciate were irrelevant to what is claimed: liquid, aqueous, pharmaceutical antibody formulations. *Supra* § IV.C.1.a. Petitioner also characterizes the claims as functional genus claims based on recitation of the term "stable" (*e.g.*, Pet. at 72), but enablement challenges to analogous claims requiring similar functionality have repeatedly failed. *E.g.*, *Fresenius*, PGR2019-00064, Paper 10 at 15-18 (upholding claims directed to a "stable" genus of pharmaceutical compositions); *Helsinn*, 2017 WL 631899, at *24 (upholding claims directed to a "stable" genus of formulations and finding that "a POSA would have used standard references to identify common pharmaceutical excipients, the universe of which that have a prior history of use in intravenous formulations is limited").

Wands Factors (2) & (3): Guidance and Working Examples in the Specification: The specification discloses stable risankizumab formulations at a pH in the range of 5.5 to 6.5 containing a detergent (e.g., polysorbate 20), both ionic and nonionic tonicity agents (e.g., sodium chloride and sorbitol), and optionally a buffer (e.g., succinate, citrate, or no buffer), at a range of different concentrations. The specification also discloses exemplary methods for evaluating the stability of the resulting formulations (e.g., AUC and SEC). *E.g.*, EX1001, Exs. 9, 12.

Petitioner nonetheless argues that the specification discloses "only two narrow examples" and "does not provide adequate guidance as to how or why the three

formulations it exemplifies are 'stable' under any set of conditions." Pet. at 74-75. As an initial matter, the number of working examples is not dispositive for enablement. *Alcon*, 745 F.3d at 1189 ("[A] patentee is not required to provide actual working examples."). Moreover, by focusing on the quantity of working examples, Petitioner again fails to consider the diversity of guidance that the disclosed formulations provide. *See supra* § IV.C.1.c.

Wands Factors (5)-(7): State of the Art, Level of Skill, and Predictability: Regarding the state of the art, Petitioner and its expert acknowledge that the specific excipient categories recited in the claims were well known, as were methods for assessing stability of pharmaceutical formulations. *See, e.g.*, Pet. at 9-11, 13, 21-22; EX1002 ¶¶ 47, 59, 99, 100, App'x B; EX2006, ¶ 95; *see also supra* § II.A. Petitioner's assertion that in 2013, there was no "FDA-approved anti-IL23p19 antibody" or an "FDA-approved formulation of Antibody A" does not establish otherwise. Pet. at 73. The claims do not require an FDA-approved formulation; the claims merely require that the formulation maintain stability suitable for its pharmaceutical application. *See supra* § IV.B.

Petitioner does not dispute that the level of skill in the art is high. Pet. at 73. Indeed, Petitioner concedes that a POSA would have had an advanced degree in a relevant discipline and at least two years of experience in developing therapeutic protein formulations. *Id*. at 33. And while Petitioner emphasizes the purported high

unpredictability in the art (*id*. at 72-74), Petitioner's evidence again consists primarily of references describing unpredictability stemming from differences among antibodies (i.e., different amino acid sequences among different antibodies). *See supra* § IV.C.1.b. Such references are inapplicable here, as the claims are directed to formulations of a ***specific antibody*** defined by specific amino acid sequences. *See id*.; *Streck*, 665 F.3d at 1291-92; *Fresenius*, PGR2019-0064, Paper 10 at 17-18 (rejecting petitioner's enablement challenges where petitioner failed to "explain sufficiently why a POSA would not have known how to adjust or select [adequate] ingredients in order to achieve the claimed stable aqueous pharmaceutical composition").

Wands Factor (8): Quantity of Experimentation Necessary: As explained above, Petitioner has not established that any experimentation would be needed to practice the claimed invention. *See supra* § IV.D.1.a. Further, Dr. Klibanov has previously testified—in stark contrast to his current testimony—that a POSA with years of antibody formulation experience would not have engaged in brute force screening of "millions" of potential formulations. Pet. at 75. Rather, he explained that starting from ***existing*** formulation studies, a POSA would have known how to "cut some corners" based on "educated guesses" and "scientific judgment" to readily arrive at other formulations within the scope of the claims as needed. EX2004, 146:19-147:10, 151:5-152:17; *see supra* § II.B. Petitioner's cited references also

describe high throughput means of screening large numbers of formulations for stability. EX1011, 132 ("The optimal combination of excipients can be found employing a ***high throughput formulation (HTF) platform*** designed to allow invasive and non-invasive screening in well plates."); *id.*, 133 ("A ***high throughput formulation*** screening can help for fast finding the most suitable excipients, such as sugars or preservatives."); EX1025, 1314 ("[T]hese [high-throughput screening] techniques can be used to examine a wider range of pH conditions, excipients, concentrations, and combinations of excipients."); *see supra* § II.B. Courts have found the use of similar techniques to support enablement. *E.g.*, *Warner Lambert*, 2007 WL 4233015, at *13 (crediting an expert's opinion that a POSA "would set up a fractional factorial design, allowing the effect of multiple formulation variables . . . to be analyzed simultaneously with a limited set of routine experiments run simultaneously").

In sum, Petitioner's *Wands* factor analysis overstates the breadth of the claims, disregards the guidance in the specification, inappropriately relies on allegations of generalized unpredictability, and disregards the evidence of record—and thus cannot satisfy its burden.

ii. Petitioner's Cited Cases Are Inapposite

Petitioner relies heavily on *Wyeth* and *Idenix*, but the presently claimed ***formulations*** are readily distinguishable from the ***method of treatment*** claims

analyzed in those cases, both involving administering ***functionally defined*** chemical compounds. In *Idenix* and *Wyeth*, the claims and specification provided no meaningful guidance as to which substituent groups or which substituent modifications should be explored to obtain a compound effective to treat the claimed conditions, and thus, the only way to practice the claimed invention was through iterative synthesis and screening of tens of thousands of compounds. *Idenix Pharms. LLC v. Gilead Sci. Inc.*, 941 F.3d 1149, 1162-63 (Fed. Cir. 2019); *Wyeth & Cordis Corp. v. Abbott Lab'y*, 720 F.3d 1380, 1384-86 (Fed. Cir. 2013). In contrast, the present claims and specification identify a specific, sequence-defined antibody, three categories of excipients that Petitioner acknowledges are well-known, and a narrow pH range to achieve a stable formulation.

Notably, formulation genus claims analogous to those challenged here have repeatedly been upheld both by the Board and district courts. In *Fresenius*, for example, the Board denied institution of an analogous enablement challenge to claims directed to "stable" pharmaceutical compositions of a specific antibody. PGR2019-00064, Paper 10 at 15-18. The *Fresenius* specification provided "a detailed disclosure of the testing used to assess stability," and the claims recited "the pH" and "specific ingredients to be included" in the claimed composition. *Id.* at 17. Both are true here.

Petitioner disregards other cases upholding functional formulation genus claims. In *Helsinn*, the court held that claims directed to pharmaceutically stable formulations of a particular active ingredient with various excipient categories were enabled where the specification disclosed three exemplary formulations. 2017 WL 631899, at *24. There, the court found that "a POSA would have used standard references to identify common pharmaceutical excipients, the universe of which that have a prior history of use in intravenous formulations is limited," that "[r]outine experimentations would have allowed a POSA to confirm the stability of these formulations," and that "[a] POSA would not have needed to make and test an unduly burdensome number of formulations in order to practice the claimed inventions." *Id.*

The court in *Warner Lambert* likewise held that claims directed to compositions of generic ACE inhibitors (a group of compounds having antihypertensive properties) and categories of stabilizing excipients were enabled where the specification disclosed examples that varied in the amounts and proportions of ACE inhibitors and stabilizers used. 2007 WL 4233015, at *13. The court observed that "[o]ne skilled in the art would set up a 'fractional factorial' design, allowing the effect of multiple formulation variables (such as five different ingredients and amounts) to be analyzed simultaneously with a limited set of routine experiments run simultaneously." *Id.*

Accordingly, Petitioner has failed to show that, under the proper legal framework, it is more likely than not that claims 7 and 19 are not enabled.

2. Other Challenged Claims

Petitioner does not raise any new or different arguments for any dependent claim. As with claims 7 and 19, Petitioner has not established that any experimentation would be needed to practice the claimed invention. *See* Pet. at 76-77. Petitioner likewise fails to establish that any alleged experimentation would be undue. *Id.* For the reasons discussed above, Petitioner therefore fails to meet the burden of establishing that any dependent claim lacks enablement. Further, dependent claims 8, 10, 15, 16, 20, 22, 27, and 28 provide additional structural elements that narrow the scope of the claimed formulations.

Claims 8, 9, 20, and 21: Claims 8 and 20 depend from claims 7 and 19, respectively, and recite that "the detergent is polysorbate 20 (PS20)." EX1001, claims 8, 20. Claims 9 and 21 further depend from claims 8 and 20, respectively, and recite that "the PS20 is present at a concentration of 0.2 mg/ml." *Id.*, claims 9, 21. These claims therefore recite a specific detergent or a specific detergent at a specification concentration.

Claims 10, 15, 16, 22, 27, and 28: Claims 10 and 22 depend from claims 7 and 19, respectively, and recite that "the formulation further comprises a buffer." *Id.*, claims 10, 22. Claims 15 and 27 depend from claims 7 and 19, respectively, and

recite that "the [osmolality] of the formulation is 200 +/- 30 mOsmol/kg." *Id.*, claims 15, 27. Claims 16 and 28 depend from claims 7 and 19, respectively, and recite that "the formulation has a pH in the range of 5.5 to 6.1." *Id.*, claims 16, 28. These dependent claims narrow the breadth of the claims and therefore decrease any experimentation deemed necessary.

Claim 14: Claim 14 depends from claim 7 and recites that "the formulation is stable following storage in a syringe for 8 weeks at 40° C." *Id.*, claim 14. The specification provides stability data obtained using these precise storage conditions. Specifically, Example 12 discloses the "[s]torage [s]tability" of Formulations 2 and 3 and provides measurements of pH, osmolality, turbidity, and percent monomer initially and after 8 weeks in storage at 40° C. *Id.*, 94:20-21, 94:26-36. Further, practicing the invention of claim 14 would not require undue experimentation simply because the claim recites an eight-week storage period. *See, e.g.*, *Falko-Gunter*, 448 F.3d at 1365 (agreeing with the Board that "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be undue in this art"). Indeed, Petitioner's cited references describe high throughput means of screening large numbers of formulations simultaneously. *Supra* § IV.D.1.b.i.

For at least these reasons, Petitioner has not established that it is more likely than not that any challenged claim is not enabled.

V. THE BOARD SHOULD DENY INSTITUTION UNDER 35 U.S.C. § 325(d)

The Board should additionally deny institution under 35 U.S.C. § 325(d) because Petitioner (1) presents the same or substantially the same arguments that were previously considered by the Office and (2) fails to demonstrate that the Office erred in a manner material to the patentability of the challenged claims. *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, at 8-9 (PTAB Feb. 13, 2020).

A. Petitioner's Written Description Arguments Are the Same or Substantially the Same as Those Raised by the Office and Overcome During Prosecution

Petitioner nowhere asserts that its written description arguments are different than those previously considered by the Office. *See* Pet. at 39-47 (discussing "material error" only). This is not surprising, as Petitioner's written description arguments repeat, often verbatim, the Examiner's written description rejection that Patent Owner successfully overcame during prosecution. Petitioner argues that the claims define the genus of antibody formulations "functionally" because they recite that the formulations are "isotonic and stable" (Pet. at 51), while the Examiner wrote that the "formulations must have specific functions, namely, the formulation must be isotonic and stable" (EX1004, 7285). Petitioner argues that the challenged claims recite "broad classes of excipients *generically*." Pet. at 51 (emphasis in original). Similarly, the Examiner characterized the claims as reciting excipients

"generically." EX1004, 7285. Petitioner alleges that the specification does not adequately describe the challenged claims because the disclosed formulations are too "narrow" (Pet. at 63), while the Examiner previously stated that the disclosed formulations were "narrow" relative to the claimed compositions (EX1004, 7625).

Consistent with this substantial similarity, Petitioner relies on references cited by the Examiner in her rejection (*e.g.*, EX1032; EX1062) and cites many of the same cases. *Compare* Pet. at 16, 28, 52, *with* EX1004, 7282-93, 7623-33. Appendix B to this paper contains a chart further aligning Petitioner's written description arguments with the written description rejection overcome during prosecution.

B. Petitioner Fails to Demonstrate that the Office Erred in a Manner Material to the Patentability of the Challenged Claims

Petitioner asserts that the Office materially erred in withdrawing its written description rejection. Pet. at 39. According to Petitioner, this "error" was allegedly "induced" by (1) Patent Owner's "mischaracterization of *Fresenius*," (2) the "duration and complexity of prosecution," and (3) the Examiner's "misunderstanding" of the scope of the claims and support in the specification. *Id*. at 39-47. As detailed below, each of these allegations is incorrect, and Petitioner fails to identify any material error in the Office's decision to allow the challenged claims.

1. Petitioner Does Not Demonstrate Error Relating to the *Fresenius* Decision

Petitioner's allegation that Patent Owner mischaracterized *Fresenius* is specious and inappropriate. *See* Pet. at 39-45. As an initial matter, Patent Owner (i) identified the patent at issue in *Fresenius* by its patent number, (ii) reproduced a representative challenged claim, (iii) accurately quoted relevant statements from the decision, and (iv) ***submitted the Fresenius decision as an attachment to its Response***.[6] EX1004, 7379, 7668, 7384-403. Given this robust disclosure, Petitioner's allegations ring hollow.

Moreover, the Examiner independently considered *Fresenius* and assessed its relevance to the then-pending claims. After *Fresenius* was first raised in prosecution (EX1004, 7373-403), the Examiner issued a final rejection explaining that the claims were not in condition for allowance (*id.*, 7621-40). That rejection specifically addressed *Fresenius*. *Id.* Only after further explanation, as well as claim narrowing by amendment—for example, by requiring a tonicity agent—did the Examiner reconsider and allow the challenged claims. EX1004, 7659-70, 7678-85.

[6] Petitioner argues that the U.S. patent at issue in *Fresenius* should also have been submitted to the PTO. Pet. at 39. Notably, the patent at issue was identified by number, and the PTO had long abandoned the requirement that copies of U.S. patents listed in an IDS should be submitted. M.P.E.P. § 609.04(a).

Petitioner nevertheless argues that Patent Owner's analogy to the claims in *Fresenius* was misleading because the *Fresenius* claims exclude mannitol, citrate and phosphate buffers, and sodium chloride. Pet. at 40-42. But the exclusion of these specific excipients does not materially change their overall scope, as they still encompass multiple categories of excipients (*e.g.*, a "sugar" and a "buffer"). EX1006, claim 1. Indeed, similar to Petitioner's argument here, the petitioner in *Fresenius* likewise asserted that the claims encompassed "millions of possible [formulations.]" Pet. at 52-53, 71-72; PGR2019-00064, Paper 10 at 12. Further, while Petitioner speculates that the excipients in *Fresenius* were carved out because they "adversely affect[ed] stability" (Pet. at 40), Petitioner ignores that each excluded excipient was used in an earlier FDA-approved formulation containing the same active ingredient (adalimumab)—a telltale sign that the carveout was intended to avoid prior art.[7] EX2007, 20.

Petitioner also argues that the disclosures in the *Fresenius* patent are significantly different than those of in '265 patent due to the inclusion of "systematic testing" of "89 distinct formulations"—differences that Patent Owner allegedly

[7] The challenged patent reported that this prior-art formulation (D-1) was at least as stable as the single formulation that fell within the claims in *Fresenius* (D-12). EX1006, cols. 31-34 (Table D-2); *Fresenius*, PGR2019-00064, Paper 10 at 12.

"failed to bring . . . to the examiner's attention." Pet. at 42-44. But written description of a claimed genus requires that the specification describe "a representative number of species ***falling within*** the scope of the genus." *Ariad,* 598 F.3d at 1350. It was undisputed that the *Fresenius* specification described ***just one species*** within the scope of the claimed genus—a fact that Sandoz omits entirely from its Petition. *Fresenius*, PGR2019-00064, Paper 10 at 12-13; *see* Pet. at 42-44. Moreover, notwithstanding Petitioner's rhetoric, Patent Owner brought the additional *Fresenius* test formulations to the '265 patent Examiner's attention. EX1004, 7379 (Patent Owner explaining that "only one" of "***dozens*** of additional test formulations" was an embodiment of the *Fresenius* claims); *id*., 7637 (the Examiner observing that "the specification [in *Fresenius*] disclosed at least one embodiment that falls within the scope of claim 1"). There is no indication that the '265 patent Examiner misunderstood the substance of the respective patent disclosures or that Patent Owner misled the Examiner.

Petitioner further argues that the Board denied institution in *Fresenius* because it rejected the petitioner's stringent construction of "stable"—and that Patent Owner's alleged failure to inform the Examiner of this was a "gross mischaracterization." Pet. at 44-45. But the Examiner was unambiguously aware of the Board's construction of "stable" in *Fresenius*, as she expressly commented that the interpretation of the term "stable" was at issue and that the Board construed

the term to have "its plain and ordinary meaning." EX1004, 7637. Further, Petitioner disregards the additional reasons for denying institution. As the Board expressly stated, and as Patent Owner explained during prosecution here, "the specification identifies with sufficient clarity each of the ingredients that must be included as part of the claimed composition." *Fresenius*, PGR2019-00064, Paper 10 at 13; *id*. at 17; EX1004, 7379.

Petitioner presents no evidence that Patent Owner mischaracterized *Fresenius* or that the Office materially erred. While Petitioner may disagree with the Examiner's decision on written description, that does not constitute an error material to patentability. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 9.

2. Petitioner Does Not Otherwise Demonstrate Material Error

Petitioner attempts to concoct material error based on certain events recorded in a summary of an interview with prosecution counsel. Pet. at 45-47. The pertinent part of the Examiner's one-paragraph interview summary states as follows:

> A discussion was held regarding the 112(a) rejection over claims 37 and 49 [issued as claims 7 and 19]. The Attorney stated that examples 9, 11 and 12 provide examples of various formulations that fall within the scope of the claims and have the claimed functional characteristics. The Attorney stated that anti-IL-23p19 antibody recited in the claims is self-buffering, and this characteristic contributes to the stability of the antibody in the various

> formulations. The Attorney proposed amending the claims to state that the formulation includes a tonifier and a buffer. The Examiner stated that these amendments would be sufficient to overcome the rejection. The Examiner also suggested amending the claims to recite the specific detergent (polysorbate).

EX1004, 7656. As explained below, Petitioner's arguments are unfounded.

a. Allowing the Challenged Claims to Include "a Detergent" Was Not Material Error

Petitioner first argues that it was material error not to require Patent Owner to limit the claims to the detergent polysorbate. Pet. at 45. But, as stated in the last sentence of the excerpt above, this was a suggestion, not a requirement. EX1004, 7656. That the Examiner once "suggested" amending the claims to recite polysorbate does not indicate that the issued claims lack written description support. *Supra* § IV.C. Nor does it suggest that the Examiner was confused by the "complexity of prosecution." Pet. at 45. Indeed, when Patent Owner introduced narrowing claim amendments following this interview, Patent Owner explained that the amended claims required "a detergent, a tonicity agent, and optionally a buffer"—not polysorbate. EX1004, 7666. The Examiner accepted that explanation, acknowledging in the Notice of Allowance that the claimed formulations comprised "a detergent" and "a tonicity agent." *Id*., 7683-84.

b. There Was No "Misunderstanding" as to Claim Scope and Disclosures

Petitioner next argues that it was material error to allow the claims in view of Patent Owner's "mischaracterization that the examples in its summary table and remarks were all within the scope of the claims." Pet. at 45-46. This argument refers to the second sentence in the interview summary excerpted above, which states that "examples 9, 11, and 12 provide examples of various formulations that fall within the scope of the claims and have the claimed functional characteristics." EX1004, 7656. Given the brevity of the summary, however, it was reasonable for the Examiner to summarize how the disclosed formulations collectively support the claims as opposed to walking through each pending claim on a formulation-by-formulation basis.

Further, in its subsequent exchanges with the Office, Patent Owner was clear that the formulation in Example 9 contained "no surfactant" (i.e., no detergent), and there is no indication the Examiner mistakenly believed otherwise. EX1004, 7666; *see also id.*, 7633 (the Examiner focusing on Formulations 2 and 3). Further, while Petitioner contends that "only Formulations 2 and 3 are within the scope of certain claims" (Pet. at 46), Petitioner ignores the statement in the '265 patent that Formulation 1 "is suitable for intravenous administration," consistent with the plain and ordinary meaning of "stable." EX1001, 92:11-45; *supra* § IV.B.

Mere disagreement with the Examiner's decision to allow the claims does not constitute material error. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 9.

3. None of the "New" Evidence Warrants Reconsideration

With essentially no explanation, Petitioner contends that "new" evidence warrants revisiting the Office's careful examination. Pet. at 38-39, 47. It does not.

EX1063 and Boehringer's Publications: EX1063 is an excerpt from the prosecution history of European Application No. 17208896.5. Petitioner does not explain how this alleged new evidence is relevant to discretionary denial. *See* Pet. at 39. Notably, Dr. Klibanov declared that the statements made during European prosecution were "similar" to statements made to the Office. EX1002 ¶¶ 144-45. For the same reason, Boehringer's publications, which, according to Petitioner, discuss "the state of the art" (Pet. at 39), are cumulative to references submitted to the Office. *See, e.g*., EX1001, item (56); EX1014.

EX1002 (the Klibanov declaration). An expert declaration is not a "super-factor" that overrides the Board's statutory discretion to deny institution. *See Boragen, Inc. v. Syngenta Participations AG*, IPR2020-00124, Paper 18 at 4-5 (PTAB Aug. 10, 2020). This is particularly true here, as Dr. Klibanov's declaration rehashes the same arguments already considered by the Office. *See Edge Endo, LLC v. Michael Scianamblo*, IPR2018-01321, Paper 15 at 19 (PTAB Jan. 14, 2019) ("we do not find that inclusion of a declaration reflecting an opinion that the Examiner

'overlooked' something in McSpadden warrants a reconsideration of the McSpadden challenges as raised by Petitioner"); *Regeneron Pharms., Inc. v. Kymab Ltd.*, IPR2019-01579, Paper 9 at 18 (PTAB Mar. 20, 2020) ("[T]he fact that the Declaration of Petitioner's expert was not before the Examiner during prosecution does not itself demonstrate that the Examiner erred.").

As such, none of the alleged "new" evidence warrants reconsideration of the Office's decision to allow the challenged claims.

C. Petitioner's Enablement Arguments Are Substantially the Same as Those Overcome During Prosecution

Petitioner further argues that discretionary denial is not warranted because the Office did not previously consider enablement. Pet. at 47. But the Examiner was required to evaluate compliance with ***every statutory requirement*** for patentability. *See* M.P.E.P. § 2103 ("Under the principles of compact prosecution, each claim should be reviewed for compliance with every statutory requirement for patentability in the initial review of the application."). Consistent with this, the record indicates that the Office did, in fact, evaluate enablement. In particular, the Examiner acknowledged during prosecution that 35 U.S.C. § 112, first paragraph, imposes two separate requirements, written description and enablement, and rejected the then-pending claims only for written description. EX1004, 7292, 7632. The facts and

the law therefore reveal that the Office previously concluded that the specification enables a POSA to make and use the claimed invention.

Petitioner also cannot avoid discretionary denial by repackaging the Office's written description rejection in the context of enablement. *See Boehringer Ingelheim Animal Health USA Inc. v. Kansas State Univ. Rsch. Found.*, PGR2022-00021, Paper 9 at 19-20 (PTAB Jul. 15, 2022) (denying institution under § 325(d) because "Petitioner's enablement challenge is largely redundant to the Examiner's rejection based on lack of adequate written description"); *Triplet Therapeutics, Inc. v. Board of Supervisors of Louisiana State Univ*., PGR2021-00059, Paper 12 at 33-40 (PTAB Sep. 8, 2021) (denying institution under § 325(d) because Petitioner's written description arguments were substantially the same as those considered by the Office in the context of an enablement rejection); *Pharmacosmos A/S v. American Regent, Inc*., PGR2020-00009, Paper 17 at 27-29 (PTAB Aug. 14, 2020) (denying institution under § 325(d) because the issues raised by petitioner's written description challenge had "substantial overlap" with those previously considered in an enablement rejection); *Novartis Pharms. Corp. v. Plexxikon, Inc*., IPR2018-01287, Paper 17 at 8-15 (PTAB Jan. 16, 2019) (denying institution under § 325(d) because "Petitioner relies on substantially the same arguments with respect to whether [a provisional application] provides § 112 support for the challenged claims as those considered by the Examiner during prosecution").

Here, Petitioner's enablement arguments are substantially the same as those previously considered by the Office in the context of written description. Specifically, Petitioner's enablement arguments are premised on its characterization of the challenged claims as "functional" and the specification as disclosing "narrow" examples, which, according to Petitioner, are not sufficient in light of the "unpredictability" in the art. *See* Pet. at 71-72, 75. As set forth in Table 2 below, these are substantially the same contentions overcome during prosecution.

Petition	**File History**
Wands Factor 8 (Pet. at 71-72): "claims 7 and 19 *generically* recite components of a *functionally* defined genus"	EX1004, 7624-25: "Claims 37 and 49 [issued as claims 7 and 19] *generically* recite a formulation comprising an anti-IL-23p19 antibody and a detergent. The formulation must have specific *functions*, namely the formulation must be stable and isotonic."

Petition	File History
Wands Factor 7 (Pet. at 72-73): "The stability of antibody formulations, particularly liquid ones, is *unpredictable.*"	EX1004, 7630: "formulating proteins, particularly antibodies, is *unpredictable*"
Wands Factor 6 (Pet. at 73): "A POSA . . . would not be able to *predict* formulation stability *a priori*"	EX1004, 7631: A POSA "would not be able to accurately *predict* if the claimed composition would result in a stable and isotonic protein formulation"
Wands Factor 5 (Pet. at 73): "The *prior art* was not developed."	EX1004, 7684: "[T]he *prior art* does not disclose formulating the claimed IL-23p19 [antibody] in any specific manner."
Wands Factor 4 (Pet. at 74): "Making stable antibody formulations was . . . a complex and *unpredictable* undertaking"	EX1004, 7631: "generating stable pharmaceutical protein formulations suitable for human administration is highly *unpredictable*"

Petition	File History
Wands Factor 3 (Pet. at 74-75): "There is *insufficient guidance* in the specification for how to identify formulations that would be stable."	EX1004, 7633: "Given the state of the art teaches that formulating liquid protein formulations is unpredictable coupled with the *lack of guidance* in the specification"
Wands Factor 2 (Pet. at 75): "The specification offers three *narrow* examples but claims a *genus* encompassing millions of formulations"	EX1004, 7625: "The specification provides no evidence that the *generic composition* of claims 37 and 49 . . . will also possess the same functional properties as the *narrow* species formulations"
Wands Factor 1 (Pet. at 74-75): "[a] laborious *trial-and-error* undertaking"	EX1004, 7629, 7627: "proteins have to be evaluated on a *case-by-case* basis" "development of a liquid protein formulation often *requires screening* of

Petition	File History
	many excipients and their combinations at different pHs"

Table 2. Comparison between Petitioner's enablement arguments and the Examiner's written description rejection and analysis

As such, "the Examiner considered the factual issue" underpinning Petitioner's enablement arguments, as evidenced by "the Examiner's rejection language, which speaks to the scope of the claims, teachings of the specification, and the [disclosed] examples." *See Triplet Therapeutics*, PGR2021-00059, Paper 16 at 4-8. Because Petitioner identifies no material error leading to allowance of the '265 patent, discretionary denial is warranted. *See* Pet. at 47; *supra* § V.B; *see Pharmacosmos*, PGR2020-00009, Paper 17 at 27-29 (denial warranted because petitioner's written description ground overlapped with the Office's enablement rejection and petitioner identified no material error).

In view of the foregoing, the Board should discretionarily deny institution under 35 U.S.C. § 325(d).

VI. PETITIONER HAS NOT MET ITS BURDEN OF ESTABLISHING ELIGIBILITY FOR POST-GRANT REVIEW

Post-grant review is available only for patents that contain or at one point contained at least one claim with an effective filing date of March 16, 2013, or later.

Instrumentation Lab'y Co. v. HemoSonics LLC, PGR2019-00047, Paper 8 at 2 (PTAB Oct. 24, 2019). Petitioner bears the burden of demonstrating eligibility for post-grant review. *Id.* at 8.

Petitioner has not met that burden. Although the '265 patent was treated as a transition application and examined under the AIA (EX1004, 5415-16, 5668), the Office's determination of the AIA status of a challenged patent during prosecution is not dispositive in determining PGR eligibility. *See Commonwealth Sci. & Indus. Rsch. Org. v BASF Plant Sci. GmbH*, PGR2020-00033, Paper 11 at 8-9 (PTAB Sept. 10, 2020). The '265 patent claims priority to U.S. Provisional Application No. 61/642,032, filed May 3, 2012. EX1001, item (60). Petitioner contends that this provisional application does not adequately describe or enable claim 14 of the '265 patent (and once-pending claim 44, which issued as claim 14). *See* Pet. at 49. But Petitioner does not separately analyze the provisional application, stating only that it "contains no more disclosure than the '265 patent itself." *Id.*; EX1002 ¶ 3. Because Petitioner fails to show that claim 14 is not adequately described and enabled by the '265 patent (*see supra* § IV), Petitioner also fails to show that claim 14 is not adequately described and enabled by the provisional application. Petitioner's sole basis for PGR eligibility therefore also fails, and the Board should deny institution for at least this separate reason. *See Instrumentation*, PGR2019-00047, Paper 8 at 3, 28.

VII. CONCLUSION

For these reasons, the Board should deny institution of the Petition.

Respectfully submitted,

Dated: August 11, 2022

/William B. Raich/
William B. Raich
Reg. No. 54,386

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I, William B. Raich, certify that **Patent Owner's Preliminary Response** contains 15,344 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

Dated: August 11, 2022

/William B. Raich/
William B. Raich
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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** and **Exhibits 2001-2007** were served electronically via email on August 11, 2022, in their entirety on the following:

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Appendix A

Excipients Identified by Dr. Klibanov	Excipients in FDA-Approved Monoclonal Antibody Liquid Formulations as of 2012
Detergents	
• **Polysorbate 80** • **Polysorbate 20** • Cremophor EL • Desoxycholate sodium • Lecithin • Polyoxyethylated fatty acids • PEG 40 castor oil • PEG 60 castor oil • Poloxamer 188 (Pluronic F68) • Sodium dodecyl sulfate • Triton X-100 EX1002 ¶ 47, App'x B; *see also* EX1015, 291 (Table II)	• **Polysorbate 20** o Avastin (0.4 mg/ml), Lucentis (0.01 mg/ml), Perjeta (0.02 mg/ml), Prolia (0.01 mg/ml), Raxibacumab (0.2 mg/ml) • **Polysorbate 80** o Actemra (0.5 mg/ml), Campath (0.1 mg/ml), Humira (1 mg/ml), Orthoclone (0.2 mg/ml), ReoPro (0.01 mg/ml), Rituxan (0.7 mg/ml), Soliris (0.2 mg/ml), Stelara (0.04 mg/ml), Tysabri (0.2 mg/ml), Yervoy (0.1 mg/ml), Zenapax (0.2 mg/ml) • Detergent concentration range: 0.01 mg/ml to 1.0 mg/ml *See* EX1014, 2-4 (Table 1), 16-17; EX1008, 697 (Table 1); EX1010, 6 (Table 2)

Excipients Identified by Dr. Klibanov	Excipients in FDA-Approved Monoclonal Antibody Liquid Formulations as of 2012
Tonicity Agents	
• **Glycine** • **Maltose** • **Mannitol** • **Potassium chloride** • **Sodium chloride** • **Sorbitol** • **Sucrose** • **Trehalose** • Calcium chloride • Magnesium sulfate • Magnesium chloride • Sodium succinate • Sodium sulfate • Sodium cholesteryl sulfate • Glucose	• **Glycine** o Raxibacumab (240 mM) • **Maltose** o Bexxar (292 mM) • **Mannitol** o Humira (66 mM), Yervoy (55 mM) • **Potassium chloride** o Campath (3 mM) • **Sodium chloride** o Arzerra (100 mM), Bexxar (145 mM), Campath (137 mM), Erbitux (145 mM), Humira (105 nM), Orthoclone (147 mM), ReoPro (150 mM), Rituxan (154 mM), Soliris (150 mM), Tysabri (140 mM), Yervoy (100 mM), Zenapax (78 mM) • **Sorbitol** o Prolia (26 mM), Xgeva (25 mM)

Excipients Identified by Dr. Klibanov	Excipients in FDA-Approved Monoclonal Antibody Liquid Formulations as of 2012

• Histidine
• Imidazole
• Inositol
• Lactose
• Alanine
• Arginine
• Asparagine
• Aspartic acid
• Threonine
• Serine
• Proline
• Glycerin
 	
EX1002 ¶ 62, App'x B; *see also* EX1015, 296 (Table VIII)
	• **Sucrose**
	  ○ Actemra (146 mM), Perjeta (120 mM), Raxibacumab (29 mM), Stelara (222 mM)
	• **Trehalose**
	  ○ Avastin (159 mM), Lucentis (26 mM)
	
	• Tonicity agent concentration range: 3 mM to 292 mM
	
	See EX1014, 2-4 (Table 1), 16-17; EX1008, 697 (Table 1); EX1010, 6 (Table 2)

Buffers	

Excipients Identified by Dr. Klibanov	Excipients in FDA-Approved Monoclonal Antibody Liquid Formulations as of 2012
• **Sodium acetate / acetic acid** • **Citric acid / monosodium citrate** • **Histidine / histidine HCl** • **Monobasic sodium phosphate / dibasic sodium phosphate** • **Sodium succinate / disodium succinate** • Glycine / glycine HCl • Sodium benzoate / benzoic acid • Sodium bicarbonate / sodium carbonate • Glucono delta lactone • Lactic acid / sodium lactate	• **Sodium acetate / acetic acid** o Arzerra (40 mM), Perjeta (20 mM), Prolia (17 mM), Xgeva (18 mM) • **Citric acid / monosodium citrate** o Humira (7 mM), Raxibacumab (12 mM), Rituxan (25 mM) • **Histidine / histidine HCl** o Lucentis (10 mM), Perjeta (20 mM), Stelara (5.5 mM) • **Monobasic sodium phosphate / dibasic sodium phosphate** o Actemra (15 mM), Avastin (57 mM), Bexxar (10 mM), Campath (12 mM), Erbitux (10 mM), Humira (14 mM), Orthoclone (17 mM), ReoPro (10 mM), Soliris (16 mM), Tysabri (10 mM), Zenapax (67 mM) • **Sodium succinate / disodium succinate** • Tris HCl o Yervoy (20 mM) • Buffer concentration range: 5 to 67 mM

Excipients Identified by Dr. Klibanov	Excipients in FDA-Approved Monoclonal Antibody Liquid Formulations as of 2012
• Tartaric acid / sodium tartrate EX1002 ¶ 51, App'x B; *see also* EX1015, 295 (Table VII)	*See* EX1014, 2-4 (Table 1), 16-17; EX1008, 697 (Table 1); EX1010, 6 (Table 2)

Appendix B

	Petition	File History
Claims	"The claims do not specify particular excipients, but recite *broad classes* of excipients generically, encompassing *any* excipient capable of acting as 'a *detergent*,' 'a tonicity agent,' or 'a buffer.' The claims also define the genus *functionally* . . . ." Pet. at 51.	"the claims *broadly* encompass *any detergent* known in the art. This detergent, when formulated with the claimed anti-IL-23p19 antibody, must have the specific *functions* recited in the claims" EX1004, 7633.
Unpredictability	"the high *unpredictability* in the art and the variability associated with excipient-excipient and excipient-antibody interactions" *Id*. at 54. "the art is highly *unpredictable*" *Id*.	"formulating proteins, particularly antibodies, is *unpredictable*" *Id*., 7630. "generating stable pharmaceutical protein formulations suitable for human administration is highly *unpredictable*" *Id*., 7631.

	Petition	File History
	"this *unpredictable* field" *Id*. at 62.	"the state of the art teaches that formulating liquid protein formulations is *unpredictable*" *Id*., 7633.
State of the Art	"the *prior art* does not disclose any specific anti-IL23p19 antibody formulations" *Id*. at 62.	"the *prior art* does not disclose formulating the claimed IL-23p19 [antibody] in any specific manner" *Id*., 7684.
Representative Number of Species	"The specification does not describe a *representative* number of species within the genus of formulations" *Id*. at 53. "three *narrow* examples are not a *representative* number of species sufficient to convey possession" *Id*. at 58.	"the specification fails to provide a *representative* number of species" *Id*., 7625. "The specification provides no evidence that the generic composition of claims 37 and 49 . . . will also possess the same functional properties as the *narrow* species formulations." *Id*., 7625.

	Petition	File History
	"two *narrow* examples are insufficient to describe a *representative* number of species within this genus" *Id*. at 63.	"The species disclosed are not *representative* of the genus because the genus is highly variant." *Id.*, 7633.
Common Structural Features	"the '265 patent fails to describe *any correlation between the structure . . . and the function*" *Id*. at 59. "a POSA would know that the stability of a particular liquid antibody formulation is not *predictable* a priori" *Id*. at 60-61.	"the genus of compositions comprising an anti-IL-23p19 antibody and a detergent that is stable and isotonic has *no correlation between its structure and function*" *Id*., 7625. A POSA "would not be able to accurately *predict* if the claimed composition would result in a stable and isotonic protein formulation" *Id*., 7631.