Filed on behalf of: Coherus BioSciences, Inc. Paper ____

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI USA, LLC and FRESENIUS KABI SWISSBIOSIM GmbH,
Petitioners,

v.

COHERUS BIOSCIENCES, INC.,
Patent Owner.

Case PGR2019-00064
Patent 10,155,039 B2

PATENT OWNER PRELIMINARY RESPONSE

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TABLE OF AUTHORITIES

Cases

Statutes

PATENT OWNER'S EXHIBIT LIST

EXHIBIT	DESCRIPTION
2001	Humira® Label, PHYSICIAN'S DESK REFERENCE 470-74 (Murray et. al. eds., 58th ed. 2004)
2002	Declaration of Christian Schöneich, *Swiss Pharma Int'l AG v. Biogen Idec, Inc.*, IPR2016-00915, Ex. 1002 (Apr. 15, 2016)
2003	PHARMACEUTICAL FORMULATION DEVELOPMENT OF PEPTIDES AND PROTEINS (Frokjaer & Hovgaard eds., 2000)
2004	U.S. Patent No. 8,216,583 to Krause (published Feb. 26, 2004 as WO2004/016286 and July 13, 2006 as US 2006/0153846A1)
2005	Int'l Pub. No. WO2009/073569A2 to Fraunhofer (June 11, 2009)
2006	U.S. Patent Pub. No. 2010/0278822 to Fraunhofer (Nov. 4, 2010)
2007	U.S. Patent Pub. No. 2012/0263731 to Fraunhofer (Oct. 18, 2012)

I. INTRODUCTION

Petitioners Fresenius Kabi USA, LLC and Fresenius Kabi SwissBioSim GmbH ("Petitioners") challenge claims 1-12 of Coherus BioSciences, Inc.'s ("Patent Owner") U.S. Patent No. 10,155,039 ("the '039 patent," Ex. 1001). The Petition should be denied because it fails to establish that the '039 patent is eligible for post-grant review ("PGR"). Moreover, Petitioners fail to show that it is more likely than not that at least one challenged claim is unpatentable.

The '039 patent is directed to stable aqueous pharmaceutical formulations comprising adalimumab, an anti-TNF-alpha antibody that is the active ingredient in Humira®. At the time the '039 patent was filed, Humira® was commercially available in an aqueous formulation comprising citrate and phosphate buffers, polysorbate 80, mannitol, and sodium chloride ("NaCl"). The '039 patent discloses the inventors' surprising discovery that the stability of buffered aqueous formulations of adalimumab could be improved by removing the citrate/phosphate buffer, mannitol, and NaCl used in Humira® and taught in the prior art to be important for stabilizing adalimumab. Ex. 1001, 5:5-27, 24:28-31. The '039 patent claims formulations that instead comprise adalimumab, a buffer (or specifically acetate buffer), polysorbate 80, and a sugar (or specifically sucrose), at a pH of about 5 to about 6 (or specifically 5.2), wherein the composition is free of mannitol, citrate/phosphate buffer, and NaCl.

The ’039 patent claims priority to three provisional applications, all filed before the AIA critical date (March 16, 2013). Petitioners argue that the ’039 patent is nonetheless PGR-eligible because these applications lack written description support and enablement for the challenged claims. This argument is without merit. At least U.S. App. No. 61/769,581 (“the ’581 provisional”), filed February 26, 2013, provides extensive and sufficient written description support for the claimed invention and enables a person of ordinary skill in the art (“POSA”) to make and use it without undue experimentation, satisfying 35 U.S.C. § 112 as to every claim of the ’039 patent.

The ’581 provisional reports experimental results from seventy separate formulations of adalimumab, which the inventors made and tested for stability. The inventors systematically adjusted formulation components, including testing seven different buffer systems (in addition to the citrate/phosphate buffer used in Humira®), various stabilizers (including sugars and polyols) and NaCl at varying concentrations, the presence or absence of polysorbate 80, and different pH values. The inventors then analyzed these various formulations using a mathematical and statistical method called Partial Least Square (“PLS”) modeling. PLS modeling allows one to evaluate the relative impact on stability of each component in the

formulation. Ex. 1008, 29:4-6.[1] As a result of this extensive experimentation and analysis, the inventors report conclusions that unequivocally support the claimed formulations, including:

- "the least stable formulations … were those using the citrate/phosphate combination," *id.* at 27:27-28;
- "mannitol and sodium chloride are destabilizers," *id.* at 13:2;
- "polysorbate 80 (PS80) improves thermal stability," *id.* at 13:3;
- "the optimal pH is near 5.2," *id.* at 36:27-28.

The '581 provisional expressly teaches that the inventive formulations may comprise a sugar, preferably "sucrose or trehalose." *Id.* at 14:22-23.

As detailed below, Petitioners' arguments for lack of written description and enablement essentially ignore the inventors' PLS analysis and the conclusions drawn from it, among other serious flaws in their analysis. Petitioners fail to show that the '039 patent is not entitled to the pre-AIA priority date of at least the '581 provisional. Therefore, the '039 patent is not eligible for PGR.

As an independent reason for denying institution, each of Petitioners' asserted grounds is meritless. Petitioners fail to demonstrate that the '039 patent—

[1] Petitioners cite to the exhibits' native page numbering, rather than the added PGR page numbers. For the convenience of the Board, Patent Owner does the same.

which Petitioners admit includes "voluminous" stability test results—lacks written description support or enablement for the claimed formulations. Pet. 18. As documented below, the '039 patent builds on the already ample support in the '581 provisional for the claimed invention, adding further experimental results, analyses, and conclusions that also satisfy the requirements of § 112. Petitioners' argument that the claims are indefinite based on the term "citrate and phosphate buffers" also fails. It is contradicted by the intrinsic evidence, including statements throughout the specification and the Examiner's confirmation that the allowed claims exclude the "citrate/phosphate combination." Ex. 1005, 224.

For the reasons explained in detail below, Petitioners have failed to show that the '039 patent is eligible for PGR, and further have failed to demonstrate that it is more likely than not that at least one claim is unpatentable. Coherus therefore respectfully submits that the Board should deny institution of the Petition.

II. BACKGROUND

A. The Extensive Disclosures in the '581 Provisional

The '581 provisional, filed February 26, 2013, reports extensive testing of stable adalimumab formulations, and teaches how to make and use these and additional stable formulations. The '581 provisional states that "[s]tability … can be determined by different methods, including but not limited to high performance liquid chromatography (HPLC) … including … size exclusion chromatography

(SEC)." Ex. 1008, 13:4-7. The '581 provisional explains that SEC "can provide information on both physical stability … as well as chemical stability," *id.* at 22:2-6, and states that SEC can be used to measure "bioactivity," *id.* at 13:11-12.

The specification determines the stability of *seventy* adalimumab formulations by SEC, after subjecting the formulations to accelerated stability conditions (*i.e.*, storage at 40°C for one or two weeks, or 25°C for two weeks). Ex. 1008, 26:8-9, 27:18-19, 33:2-3, 35:3-5. Reverse phase HPLC is also used to analyze stability for some of the formulations. The commercial Humira® formulation is tested as a control and comparator (formulations 15, 31, 47 and 59). Ex. 1008, 31:1-5; Ex. 2001, 470; Ex. 1001, 22:39-40 ("the commercially available formulation for Humira® was used as a control"). Many of the inventors' formulations show superior stability to Humira®.

The data from multiple formulations are then analyzed together using PLS modeling. Ex. 1008, 29:4-5, 35:9-38:10. PLS is a "multivariate statistical method that allows one to evaluate the relative impact of each component in the formulation" on, *e.g.*, stability. *Id.* at 29:5-10, *see also* 23:23-24:26. The information gleaned from this technique allows one to avoid using a brute force approach to test stability of all combinations of potential formulation components and conditions. The '581 provisional includes ten figures from PLS modeling that illustrate the effect of varying the concentrations of various excipients, and the

formulation pH, on the stability of adalimumab. *Id.* at Figs. 3-12, 29:11-30:17, 35:9-38:10. Using this technique to analyze the experimental data, the inventors determined the effect of a whole spectrum of different buffer and excipient combinations, concentrations, and pH values on adalimumab's stability. *See id.* at Figs. 3-12.

As a result of their empirical testing and PLS analysis, the inventors report several surprising discoveries, including:

- "adalimumab compositions which comprise only one buffer … are more stable than adalimumab compositions comprising both a citrate buffer and a phosphate buffer," *id.* at 12:20-26; and
- "mannitol and sodium chloride are destabilizers," *id.* at 13:2.

The '581 provisional also expressly teaches the use of acetate buffer, *id.* at 32:17-18; that the formulations "may also comprise a sugar," preferably "sucrose or trehalose," *id.* at 14:22-23; and that "the optimal pH is near 5.2," *id.* at 36:27-28.

B. The Extensive Disclosures in the '039 Patent

The '039 patent undisputedly adds dozens more examples of adalimumab formulations and stability tests over and beyond the '581 provisional. Pet. 47. These include, among other things, stable formulations with higher adalimumab concentrations and express use of acetate buffer at pH 5.2. Ex. 1001, 38:34-40 (Block E studies); 54:61-59:10 (Block H studies). Multiple additional stability

testing techniques and results are added, including capillary isoelectric focusing (cIEF), capillary electrophoresis sodium dodecyl sulfate (CE-SDS), freeze/thaw cycle results, and agitation studies. *See id.* Sixteen new figures and expanded PLS analysis of the stability data from the additional formulations and techniques are reported. *Id.* at 62:11-66:64.

As in the '581 provisional, "the commercially available formulation for Humira® was used as a control," *id.* at 22:39-40, 37:17-19, and the inventors surprisingly report that many of the inventors' formulations showed better stability than the Humira® formulation, *see, e.g.*, *id.* at 30:1-15, 58:55-61.

The '039 patent expressly states that "acetate buffer is also a suitable replacement for the citrate phosphate buffer combination." *Id.* at 21:46-47. It includes stability data for acetate-buffered formulations at pH 5.2 that are free of i) mannitol, ii) citrate and phosphate buffers, and iii) NaCl, demonstrating superior stability compared to Humira®. *Id.* at 38:34-36, 39-40 (Table E-2) (*compare* formulation 1 (Humira®) *with* formulations 9 and 11).

C. The Petition Mischaracterizes the Prosecution History and Omits Critical Portions

In summarizing the prosecution history of the '039 patent, Petitioners omit critical portions and misleadingly describe the prior art and how it was overcome by Patent Owner. The central prosecution issue, obviousness over Salfeld (Ex.

1003) and Lam (Ex. 1004), was overcome because the Examiner agreed that there would have been no reasonable expectation of success in making the claimed adalimumab formulation by removing citrate/phosphate buffers, the mannitol stabilizer, and NaCl from prior art adalimumab formulations. Ex. 1005, 176-177, 224.

Petitioners misleadingly portray Lam, stating that it "taught anti-TNF-α antibodies," and conflate this with a disclosure of adalimumab. Pet. 6. However, *Lam does not relate to adalimumab formulations*. As Patent Owner explained during prosecution, "Lam tested the stability of two humanized antibodies with non-human CDRs (rhuMab CD18 and rhuMab CD20) . . . . [b]y contrast, the present claims recite adalimumab, an antibody that binds TNF-α—not CD18 or CD20." Ex. 1005, 217, *see also* 192-193. "Salfeld is the only reference cited in the present obviousness rejection that ***mentions adalimumab***, and specifically teaches that the ***inclusion of mannitol*** in an adalimumab pharmaceutical composition is ***preferred***." *Id*. at 213 (emphasis original).

Patent Owner explained that in preparing stable antibody formulations, the *particular protein* (antibody) being stabilized in the formulation is critical to stability and, thus, the cited disclosures regarding stabilizing *other antibodies* would not have provided a POSA with a reasonable expectation of success in stabilizing adalimumab. *Id*. at 192-194 and 215-217. In emphasizing that stability

is dependent on the "specific protein" being stabilized, Patent Owner quoted Fraunhofer's statement that "the stabilizing effects of additives are **protein**- and concentration-**dependent**" to explain that it was not obvious to prepare a stable formulation of *adalimumab* by "using the formulations of Lam which contained different antibodies." *Id*. at 215 (emphasis original). Patent Owner further explained that "as neither Salfeld or Lam provide any data regarding the stability of an aqueous pharmaceutical formulation of adalimumab," there was no reasonable expectation "that the presently claimed compositions would be stable." *Id*. at 217.

In contrast to the deficient disclosures of the cited prior art, the '039 patent provides extensive experimental results, modeling, and conclusions based on PLS analysis of about ninety unique adalimumab formulations. These disclosures describe and enable stable adalimumab formulations that are free of previously required adalimumab stabilizers, *e.g.*, mannitol and the combination of citrate and phosphate buffers, and the previously used tonicity modifier, sodium chloride.

The Examiner agreed and issued a Notice of Allowance, stating:

> [T]he claims are allowable because the most pertinent prior art neither teaches nor suggests any stable antibody formulations without mannitol, ***citrate/phosphate combination*** and NaCl.
>
> … Applicant has demonstrated that the mannitol is present in the most pertinent art of record (U.S. Pat 6,090,382) and the commercial

> formulation requires mannitol. … ***but the claimed inventions shows stability without mannitol***. Note that the HUMIRA product information requires addition of mannitol.

Ex. 1005, 224 (emphasis added).

Petitioners' claim construction for the claim term "citrate and phosphate buffers" and related indefiniteness argument (Ground 3) are directly contradicted by the Examiner's recognition that the claims require a formulation free of "citrate/phosphate combination" buffers. *Id.*

III. LEVEL OF ORDINARY SKILL IN THE ART

Petitioners use an overly broad and insufficiently experienced definition for the person having ordinary skill in the art ("POSA"), namely, a Bachelor's degree "in chemistry, biochemistry, pharmaceutical sciences or chemical engineering (or a related field) with substantial practical experience in protein biopharmaceutical formulation," or an advanced degree (Master's or Ph.D.) with "somewhat less practical experience." Ex. 1002 ¶ 25. Petitioners' proposed level of skill is inappropriately low, as reflected by the prior art itself. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

A Bachelor's degree in chemistry or chemical engineering can encompass fields as distant as inks, dyes, paints, and polymer coatings, and an advanced degree in one of these disciplines with "somewhat less practical experience in

protein biopharmaceutical formulation" is too far below the ordinary level of skill in the field of biopharmaceutical formulations. Indeed, Petitioners' expert has previously asserted that a POSA involved in antibody formulation would have "a Ph.D. or other post-graduate training in protein chemistry or a related field with at least a few years of practical industrial or academic experience preparing protein formulations. The experience includes practical familiarity with assays for assessing protein stability … so as to optimize a protein formulation based on the results." Ex. 2002 ¶ 83.

Patent Owner submits that, as of 2012, the education and experience level of a POSA involved in pharmaceutical antibody formulation would have included an advanced degree in biology, biochemistry, or chemistry (or related discipline), and at least two years of experience preparing formulations of proteins suitable for therapeutic use. The POSA would have further understood stability testing and partial least squares (PLS) modeling for formulation development. Ex. 1008, 13:8-18, 23:22-33 (describing methods known in the art); *see* Ex. 2002 ¶83. A POSA also would have been aware of the prior art concerning adalimumab formulations, and would have been familiar with the commercially-available Humira® formulation.

Petitioners' failure to properly establish the level of skill of a POSA is fatal to its written description and enablement challenges, which rely upon Petitioners'

inaccurate level of skill. *See Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1376-77 (Fed. Cir. 2012) ("In this case, … the invention itself featured the meat encasement art…. Without some understanding of meat and meat encasement technology in various settings, the artisan of ordinary skill would not grasp many aspects of the invention.").

IV. CLAIM CONSTRUCTION

The claims should be given their plain and ordinary meaning in the context of the specification and prosecution history. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*). The standard for finding lexicography so as to depart from the plain meaning is "exacting." *GE Lighting Sols., LLC v. Agilight, Inc.*, 750 F.3d 1304, 1309 (Fed. Cir. 2014). "To act as its own lexicographer, a patentee must 'clearly set forth a definition of the disputed claim term,' and 'clearly express an intent to define the term.'" *Id.* (quoting *Thorner v. Sony Comput. Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012)). The Petition focuses on out-of-context statements in the specification that do not define the claim terms at issue, and improperly departs from the plain meaning of the terms.

A. "Stable aqueous pharmaceutical formulation"

The claims recite a "stable aqueous pharmaceutical formulation." This term should be given its plain and ordinary meaning. Generally, a stable aqueous

pharmaceutical formulation maintains stability suitable for its intended pharmaceutical application. *See* Ex. 1001, 9:20-23; *Silvergate Pharms. Inc. v. Bionpharma Inc.*, No. 16-876, 2018 WL 1610513, at *10 (D. Del. Apr. 3, 2018) (adopting a plain and ordinary meaning of "stable"). This term does not require the extensive testing needed for FDA approval, nor does it require stability upon "long-term storage." The specification repeatedly describes "stable" formulations of adalimumab where stability is tested using well-accepted methods, such as determining loss of monomer content by size exclusion chromatography (SEC) under accelerated stability conditions (*e.g.*, one week at 40ºC, two weeks at 40ºC, or two weeks at 25ºC). *See, e.g.*, Ex. 1001, 5:65-67, 21:8-11, 23:1-28, 30:27-36, 42:35-37, 58:61-63. A POSA would understand that at least the assays described in the specification, which use the commercial Humira® formulation as a control comparator, are sufficient to determine that an adalimumab formulation is "stable" within meaning of the claims.

The plain language of the claims does not require "long term" stability. Petitioners' attempt to graft this requirement into the claims is improper. *Phillips*, 415 F.3d at 1312 ("'[W]e look to the words of the claims themselves… to define the scope of the patented invention.'") (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). The specification describes stability during long-term storage as an embodiment of the invention, but that is insufficient

basis to import a "long-term storage" or "long term stability" requirement into the claims where it is not recited. *See Phillips*, 415 F.3d at 1323 ("[A]lthough the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments."). Indeed, the specification separately defines "long term stability," indicating that it is different from the term "stable" standing alone. Ex. 1001, 9:12–27.

Moreover, the specification describes extensive stability testing based on accelerated conditions, freeze-thaw (F/T) cycles, and agitation studies—none of which requires long term storage. *See id.* at 23:1–52:45 (accelerated conditions), 52:46–54:60 (freeze-thaw and agitation). The specification teaches use of SEC and other chromatography techniques to measure stability. *Id.* at 19:34-20:62, 30:1-36. In the context of the specification, a POSA would not read the claim term "stable" to require testing through direct measurement of "biological activity" following "long term storage." Pet. 19.

Petitioners' construction relies heavily on two alleged "definitions" in the '039 patent, both of which specifically relate to "long-term storage." *See* Pet. 10-11; Ex. 1001, 9:28–33 (defining "'stable' *with respect to long-term storage*"), 9:11–27 (defining "long-term storage" and "long term stability"). These are not definitions of the claim term "stable aqueous pharmaceutical formulation," and thus do not meet the "exacting standard" required to show lexicography. *Agilight*,

750 F.3d at 1309 ("[A] patentee must 'clearly set forth a definition ***of the disputed claim term***,' and 'clearly express an intent to define the term.'") (quoting *Thorner*, 669 F.3d at 1365) (emphasis added). The specification as a whole does not show a "clear intent" to redefine the term "stable" to require, as Petitioners assert, "a range of stabilities… [including] compositions that do not lose more than 5% of their biological activity when stored for a minimum of two years...." Pet. 12.

Petitioners' attempt to read in ranges of different limitations from the specification's description of "long-term storage" is improper and baseless. A POSA would not interpret the claims as covering a genus of formulations having a range of different stabilities as Petitioners suggest, especially because the claims simply do not recite a range of stability values to be achieved over different periods of time. Additionally, a POSA reading the description of "stable with respect to long term storage" in the '039 specification would understand that it does not define a "range of stabilities" that are all required; rather, it sets a minimum level (*i.e.*, loss of not more than 20% of activity) and notes *optional* "more preferable" levels. Ex. 1001, 9:28–33. Moreover, a POSA would understand that this definition does not apply to the '039 claims, because the claims do not require "long term storage."

B. "Buffer"

Contrary to Petitioners' argument, the specification does not define a "buffer" as "*any* substance that has *any* buffering capacity." Pet. 14. Rather, the specification distinguishes from "buffer-free" formulations in which "the protein itself is a self buffering entity." Ex. 1001, 2:32-37. Again, there is no lexicography defining this term as broadly as Petitioners suggest.

A POSA reading the specification would understand the term "buffer" has its plain and ordinary meaning, which refers to traditional buffering systems used to "introduce buffer capacity" to a pharmaceutical formulation. *Id.* The specification includes many examples of buffers, all of which are standard pharmaceutical buffers. *Id.* at 21:44-47 (discussing citrate, phosphate, histidine, succinate, tartrate, and acetate buffers). Indeed, Petitioners' expert has acknowledged in other proceedings that, before the relevant date here, "it was widely known that there were only a few buffers suitable for the 5-7 pH range for most protein formulations." Ex. 2002 ¶ 43 (citing Ex. 2003 at 12-13 (providing a short list of "buffers used in protein formulations," which includes all of the buffers disclosed in the '039 patent)).

C. "Citrate and phosphate buffers"

The claims of the '039 patent recite a formulation that is "free of … citrate and phosphate buffers," which a POSA would understand means free of the

combination of citrate and phosphate buffers. The specification extensively supports this interpretation of the claims, stating throughout that citrate and phosphate in combination are to be avoided. Ex. 1001, 5:15–27, 21:43–47; *see also infra* Section VI.C. As admitted on page 9 of the Petition, the Examiner's reasons for allowance confirm that the claims require omission of the "citrate/phosphate combination." Ex. 1005, 224. Thus, the plain and ordinary meaning in the context of the specification and prosecution history is that the formulation is "free of the combination of citrate and phosphate buffers." *See Phillips*, 415 F.3d at 1313.

D. "About"

The term "about" should be given its plain and ordinary meaning. A POSA reading the specification would understand that the term "about" should be interpreted in the context of the term with which it is used. *Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1368 (Fed. Cir. 2008) (quoting *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995)) ("[T]he use of the word 'about,' avoids a strict numerical boundary to the specified parameter. Its range must be interpreted in its technologic and stylistic context."). While the specification provides guidance as to what the term "generally mean[s]," Ex. 1001, 7:25–27, it does not support Petitioners' attempt to indiscriminately add ±20% to every number preceded by the term "about." *See* Pet. 14, 40, 54.

In particular, a POSA would not understand the phrase "a pH of about 5 to about 6" to include "pH 4 to 7.2," as Petitioners argue. Pet. 14. The specification reports pH to the tenth of a digit, explaining that "pH should preferably be *at 5 or higher* for best stability … [and] the optimal pH is *near 5.2*." Ex. 1001, 61:24–25 (emphasis added). Likewise, given this disclosure and Patent Owner's express claim to "a pH of about 5 to about 6," a POSA would not understand the claimed pH of "about 5.2" to encompass the broad range of pH 4.2–6.2. *Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs., Ltd.*, 476 F.3d 1321, 1327 (Fed. Cir. 2007) (holding "about 1:5" could not be found "to encompass a range of ratios that could potentially render meaningless another claim's limitation, namely the 1:1 limitation"). Petitioners' position also makes little sense because it leads to different ranges depending on whether the pH is acidic or basic. Under Petitioners' construction, a pH of "about 2" would have a relatively narrow range of 1.6-2.4, while a pH of "about 10" would translate to a four-point range of 8-12. A POSA would not interpret the claims in this manner.

E. Other Claim Terms

Patent Owner reserves the right to contest Petitioners' other claim constructions, provide further constructions of the terms above, and to propose additional terms for construction at a later stage in this proceeding (if any) and in any other proceedings.

V. PETITIONERS FAIL TO ESTABLISH THAT THE '039 PATENT IS A POST-AIA PATENT ELIGIBLE FOR PGR

A. Petitioners Bear the Burden of Demonstrating That at Least One Claim is Subject to the AIA

A PGR may not be instituted unless at least one claim has an "effective filing date" (as defined in 35 U.S.C. § 100(i)) on or after March 16, 2013. *See* Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), §§ 3 (n)(1), 6 (f)(2)(A). Petitioners bear the burden to prove that at least one claim is subject to the first-inventor-to-file provisions of the AIA and, therefore, eligible for post-grant review. *See, e.g.*, *Mobile Tech, Inc. v. InVue Security Prods. Inc.*, PGR2018-00004, Paper No. 15, at 5-6 (PTAB May 3, 2018). Petitioners' burden never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

Petitioners admit that the specification of the '039 patent is identical to its parent applications, Applications Nos. 14/020,733 and 15/360,678. Pet. 21. Each of these applications claims priority to, and makes reference to, three provisional applications – the '581 provisional and Provisional App. Nos. 61/698,138 and 61/770,421 – all three of which were filed prior to the AIA critical date. Ex. 1010 at 4-5, 158-183; Ex. 1011 at 490-493, 622-647. Thus, for purposes of determining whether the '039 patent is eligible for PGR, it is sufficient for any one of the three provisional applications to provide the necessary written description and

enablement support for the claims. *See* 35 U.S.C. § 119(e); *Mobile Tech, Inc.*, PGR2018-00004, Paper No. 15, at 8 ("[T]he relevant inquiry is whether any of the identified parent applications filed prior to March 16, 2013 … provide written description support for [the] claim…"). Because it is not necessary, for purposes of denying institution, to analyze the disclosures of the '138 and '421 provisionals, those disclosures are not discussed below. Patent Owner reserves the right to rely on those applications at a later stage in this proceeding (if any) and in any future proceeding.

Here, Petitioners fail to establish that any of the challenged claims (1-12) has an effective filing date on or after March 16, 2013. Because all of the challenged claims are entitled to the benefit of at least the February 26, 2013 filing date of the '581 provisional, a PGR cannot be instituted. *See* AIA §§ 3 (n)(1), 6 (f)(2)(A).

B. The '581 Provisional Adequately Describes Claims 1-12, and Petitioners Fail to Satisfy Their Burden to Prove Otherwise

Petitioners do not meet their burden of showing that the '581 provisional lacks written description support for the claims of the '039 patent. Petitioners apply an incorrect legal standard for written description and an unsupported claim construction of "stable." Moreover, Petitioners ignore the analysis of and conclusions drawn from the extensive stability testing reported in the '581 provisional.

A disclosure is sufficient if it "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date," based on an "objective inquiry into the four corners of the specification." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). Contrary to Petitioners' arguments, the Federal Circuit has repeatedly held that possession does *not* require "empirical data," actual reduction to practice, or working examples. Pet. 33, *see also* 22, 27.

> *There is no rigid requirement that the disclosure contain 'either examples or an actual reduction to practice*;' the proper inquiry is whether the patentee has provided an adequate description that 'in a definite way identifies the claimed invention' in sufficient detail such that a person of ordinary skill would understand that the inventor had made the invention at the time of filing.

Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293, 1308 (Fed. Cir. 2015) (quoting *Ariad*, 598 F.3d at 1352) (emphasis added); *Nuvo Pharms. v. Dr. Reddy's Labs.*, 923 F.3d 1368, 1380 (Fed. Cir. 2019) ("[O]ur case law does not require experimental data demonstrating effectiveness…. Moreover, we have repeatedly stated that the invention does not actually have to be reduced to practice.").

For claims reciting a genus, sufficient description "requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the

art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1349-1350. A number of factors are considered in evaluating the adequacy of disclosures supporting generic claims, including "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue." *Id*. at 1351.

As demonstrated below, the '581 provisional easily demonstrates that the inventors possessed the invention claimed in the '039 patent.

1. The '581 Provisional Describes the Formulations of Claims 1-12, Including "Stable" Formulations.

a. The '581 Provisional Describes Every Element of the Claimed Invention

The '581 provisional discloses stable formulations of adalimumab, and, based on PLS analysis of the tested formulations, teaches the formulation components that will result in *additional* stable formulations. The '581 provisional and its original claims disclose every element of the claimed invention, as illustrated in the following claim chart.[2]

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[2] Claims 5-8 are identical to claims 1-4, but recite "sucrose" instead of "sugar." Claims 9-12 are identical to claims 5-8, but recite "acetate buffer" instead of "a buffer." These claims are further addressed in Sections V.B.2 and V.B.3 below, respectively.

10,155,039 patent claims		**'581 provisional disclosures (Ex. 1008)**
1	1. A stable aqueous pharmaceutical composition comprising: a) adalimumab; b) a buffer;	Claim 1. "A stable aqueous pharmaceutical composition comprising adalimumab and a single buffer." Ex. 1008, 39. "Buffers that may be suitable for purposes of the invention include but are not limited to succinate, histidine, citrate, phosphate, tartrate, and maleate." *Id.* at 13:24-25; *see also* 32:17-20 (Example 2, describing adalimumab formulations comprising acetate buffer).
	c) polysorbate 80; and	Claim 7. "The composition of claim 6 [ultimately dependent from claim 1], wherein said polysorbate is polysorbate 80." *Id.* at 39; "[P]olysorbate 80 (PS80) improves thermal stability." *Id.* at 13:3; "PS80 is a potent stabilizer for protecting adalimumab against thermal stress…" *Id.* at 37:9-10.
	d) a sugar	Claim 11. "The composition of any of the preceding claims, further comprising a sugar." *Id.* at 39; Claim 12. "…wherein said sugar is selected from the group consisting of sucrose and trehalose." *Id.*; *see also* 3:28-29, 14:22-23.
	wherein the composition is free of i) mannitol, ii) citrate and phosphate buffers, and iii) sodium chloride and	"[M]annitol and sodium chloride are destabilizers." *Id.* at 13:2, *see also* 37:26-29. "The use of NaCl as a tonicity modifier reduces the stability of adalimumab in aqueous solution when stored at 25 ºC or 40 ºC." *Id.* at 28:6-8. "[W]hen citrate and phosphate buffer are used together, the formulation is least stable." *Id.* at 36:3-4, *see also* 27:26-31, 30:10-11, 31:9–11.

	wherein the composition has a pH of about 5 to about 6.	Claim 3. "The composition of any of the preceding claims, wherein said composition has a pH of about 5 to about 6." *Id.* at 39; "… pH should preferably be at 5 or higher for best stability. … the stability appears to be maximal near pH 5.2, falling off at a higher and lower pH." *Id.* at 36:26-31, *see also* 13:29-31, Fig. 7, Fig. 8.
2, 4	2 [and 4]. The composition of claim 1 [claim 3], wherein the composition has osmolality of about 180 to 420 mOsM;	" [T]he osmolality of the provided formulations is from about 180 to about 420 mOsM." *Id.* at 16:1-2.
	the composition is suitable for administration to a subject as a single dose; and the dose contains about 40 mg of adalimumab.	"In one embodiment, adalimumab is administered at 40 mg by a single subcutaneous (SC) injection." *Id.* at 18:18-19.
3	3. The composition of claim 1, wherein the pH is about 5.2.	"[T]he pH … even more preferably is about 5.2." *Id.* at 13:29-31; "[T]he stability appears to be maximal near pH 5.2, falling off at a higher and lower pH." *Id.* at 36:30-31.

The original claims above "show that the applicants recognized and were claiming" the same stable formulations now claimed in the '039 patent, including adalimumab, a buffer, polysorbate 80, and a sugar (specifically sucrose), at a pH of about 5 to about 6. *Mentor Graphics Corp. v. EVE-USA, Inc.*, 851 F.3d 1275, 1297 (Fed. Cir. 2017) (quoting *Crown Packaging Tech., Inc. v. Ball Metal Beverage Container Corp.*, 635 F.3d 1373, 1381(Fed. Cir. 2011)) (alterations

omitted). Moreover, the specification of the '581 provisional includes extensive description of appropriate components for stable adalimumab formulations, experimental results, and PLS modeling demonstrating stability of a wide variety of formulations, as discussed below. Petitioners fail to carry their burden of establishing that the '581 provisional does not demonstrate possession of the claimed formulations.

As a preliminary matter, Petitioners and their expert, Dr. Schöneich, fail to acknowledge that the commercial Humira® formulation is used as a control in each stability experiment reported in the '581 provisional. A POSA would recognize that the first formulation in each experiment (formulations 15, 31, 47, and 59) is the same Humira® formulation that was commercially available at the time of the invention. Ex. 1008, 31:1-5 (noting formulation 15 is the Humira® formulation); Ex. 2001, 470; *see also* Ex. 1001, 22:39-40 ("the commercially available formulation for Humira® was used as a control"). Petitioners do not contend that the FDA-approved Humira® formulation is not stable. To the contrary, Dr. Schöneich has testified previously that he would expect "FDA-approved drug[s] … to maintain stability over a suitable shelf-life." Ex. 2002 ¶ 97.

Because of Dr. Schöneich's failure to acknowledge that the '581 provisional reports a wide variety of formulations that surprisingly performed *as well as or better than* Humira® in stability tests, the Petition is not supported by any credible

evidence regarding whether a POSA would not have understood from the '581 provisional that the inventors possessed "stable" adalimumab formulations. *See Alcon Research Ltd. v. Barr Labs, Inc.*, 745 F.3d 1180, 1191-92 (Fed. Cir. 2014) (holding that where defendant "adduced no evidence…that was probative of" how a POSA would have understood the patent disclosures, "there was no basis on which to find a lack of adequate written description").

The '581 provisional systematically tests the stability of adalimumab with *seven* different single buffer systems (citrate, phosphate, succinate, histidine, tartrate, maleate, and acetate) and compares them to the citrate/phosphate buffer system used in the commercial Humira® formulation. Ex. 1008, 24-26 (Tables 1A-1D), 30-31 (Tables 1G-1H), 32-33 (Tables 2A-2B). Based on these results, the '581 provisional concludes that adalimumab formulations comprising these buffers "are more stable than adalimumab compositions comprising both a citrate buffer and a phosphate buffer." *Id*. at 12:22-23. This discovery was "very unexpected in view of the teachings of the prior art … which emphasized the importance of the dual citrate/phosphate buffer system … [or taught] to exclude a buffer." *Id.* at 12:23-24.

The '581 provisional also reports stability data for formulations containing various sugars and sugar alcohols (mannitol, sorbitol, trehalose), with and without NaCl. *Id.* at 25-26 (Tables 1C-1D), 28-29 (Table 1F), 32-33 (Tables 2A-2B).

Different concentrations of these components are also tested. *Id.* at 26-29 (Tables 1D-1F, testing 65 mM and 240 mM concentrations of mannitol, sorbitol, and trehalose, and 100 mM, 150 mM, 35 mM, and 60 mM NaCl). The inventors conclude from this testing that "sorbitol and trehalose appear to be *better stabilizers than mannitol* when used at higher concentrations," and "NaCl as a tonicity modifier reduces the stability of adalimumab." *Id.* at 28:5-8 (emphasis added). Likewise, they expressly conclude that "*mannitol and sodium chloride are destabilizers*." *Id.* at 13:2 (emphasis added); *see also id.* at 37:26. The '581 provisional also teaches including a sugar, preferably "sucrose or trehalose," in the formulation. *Id.* at 3:28-29, 14:22-23.

The '581 provisional reports stability data for a variety of formulations with and without 0.1% polysorbate 80. *Id.* at 26 (Table 1D), 28-29 (Table 1F), 32-33 (Tables 2A-2B). Based on PLS analysis of the results, the inventors conclude that "polysorbate 80 (PS80) improves thermal stability," *id.* at 13:3, and "PS 80 is a potent stabilizer," *id.* at 37:9-10.

The '581 provisional also reports stability tests studying the effect of varying the pH. In Example 2, twelve different "compositions at pH of 5.2 and 3.5 were tested," including the commercial Humira® formulation (formulation 47). *See id.* at 32-33 (Tables 2A-2B). The stability tests demonstrate that all of the formulations at pH 5.2 were stable: formulations 47, 49, 55, and 57 retain greater

than 98% monomer content by SEC measurement, and formulations 49, 55, and 57 exhibit stability comparable to or better than the Humira® formulation 47. *Id.* On the other hand, "formulations at pH of 3.5 quickly lose their stability." *Id.* at 33, *see* Table 2B (reporting monomer contents of less than 80% following one week at 40 °C ("SEC t1") for formulations at pH 3.5). The inventors conclude that "formulations at pH 5.2 are much more stable than formulations at pH 3.5." *Id.* at 33. The '581 provisional also repeatedly teaches adalimumab formulations with a pH of "about 5 to about 6," and preferably "near 5.2." *Id.* at 36:20-31; *see also* 3:9-10, 13:29-31, 39 (claim 3).

The specification also demonstrates that formulation 42—which Petitioners admit is within the scope of at least claim 1—displays stability comparable to the commercial formulation of Humira® (formulation 31). *Id.* at 28-29 (Table 1F); Pet. 35. Indeed, all of the formulations tested in the '581 provisional, with the exception of those at pH 3.5, display stability comparable to or better than the commercial Humira® formulation (formulations 15, 31, 47, 59). *See* Ex. 1008, 28-29 (Tables 1E-1F), 33-35 (Tables 2B, 3A-3B). In all experiments, all formulations at pH 5.2 retained greater than 98% monomer content (measured by SEC) following storage under accelerated conditions. *See id.*

While the invention of stable formulations that do not comprise citrate/phosphate buffers, mannitol, or NaCl would not have been expected based

on the prior art, *see id.* at 12:20-26, the inventors' possession of such formulations is clearly demonstrated by the extensive test results and PLS analysis discussed above. This case is thus readily distinguishable from *Nuvo Pharmaceuticals*, where the Federal Circuit found a lack of written description because "the specification provide[d] *nothing more than the mere claim* that [the claimed invention] might work, *even though persons of ordinary skill in the art would not have thought it would work*." 923 F.3d at 1381 (emphasis added). *Nuvo Pharmaceuticals* itself distinguishes cases where "accelerated stability testing data" supported a stability claim, and where the specification contained "experimental results for similar drug formulations demonstrating a trend in their clinical effectiveness, even if the data were not specifically related to the exact formulation claimed." *Id.* at 1382-83 (distinguishing *Alcon*, 745 F.3d at 1184 and *Allergan*, 796 F.3d at 1309).

In sum, the '581 provisional expressly teaches each element of the claimed formulation: adalimumab comprising a buffer (including acetate buffer), polysorbate 80, and a sugar (including sucrose), with a pH of about 5 to about 6 (preferably 5.2), wherein the composition is *free of* identified destabilizers: mannitol, citrate and phosphate buffers, and NaCl. It describes the preferred concentrations of these components. Ex. 1008, 3:1-3 (adalimumab), 3:6-8 (buffer), 16:1-11 (tonicity modifier, *e.g.*, sucrose), 37:9-12 (PS80). These teachings are

backed by accelerated stability data and mathematical analysis that correlate these "structural features" (*i.e.*, known formulation components) with the result of a "stable" adalimumab formulation. *Ariad*, 598 F.3d at 1349-1350 (holding written description of a genus may be satisfied by teaching "structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus"). This is ample written description of the claimed invention.

The disclosure of the '581 provisional is more extensive than the disclosure found sufficient in *Alcon*. 745 F.3d at 1190-92 (reversing finding of lack of written description). As in *Alcon*, the '581 provisional "provides exemplary formulations that embody the claimed invention, reciting concentrations of every ingredient." *Id.* at 1191. The '581 provisional "discloses data … from accelerated stability testing" demonstrating that claimed formulation components perform as well or better than the known Humira® formulation, and describes the additional formulation components to which the disclosure is understood to relate, including disclosure of the preferred types and concentrations of each component. *Id.*

Additionally here, the '581 provisional provides extensive PLS analysis correlating the presence or absence of specific formulation components with stability. This is an identification of the "structural features" of stable adalimumab

formulations that satisfies the test for written description. *See Ajinomoto Co., Inc. v. ITC*, 932 F.3d 1342, 1360 (Fed. Cir. 2019).

Thus, the '581 provisional demonstrates that the inventors conceived of and described the claimed invention at the time the '581 provisional was filed—including the idea that omitting the mannitol, citrate/phosphate buffers, and NaCl used in Humira®, and including polysorbate 80, sugar, and pH 5.2, would improve stability. *See Alcon*, 745 F.3d at 1191.

b. Petitioners Rely on an Incorrect Legal Standard for Written Description

Petitioners incorrectly argue that the '581 provisional lacks sufficient written description for the claimed formulations by focusing myopically on the "specific examples" and formulations for which stability is demonstrated "by presenting test data." Pet. 22, *see also* 26-27 (analyzing whether Table 2A includes a specific formulation that meets every element of the claims), 30-31 (arguing "the application does not describe a specific formulation containing sucrose"); 33 (alleging the "applications *must describe empirical data*" demonstrating "the claimed degree of stability") (emphasis added).

The Federal Circuit has repeatedly held that the specification need not contain "either examples or an actual reduction to practice." *Allergan*, 796 F.3d at 1308 (quoting *Ariad*, 598 F.3d at 1352); *Falko-Gunter Falkner v. Inglis*, 448 F.3d

1357, 1366 (Fed. Cir. 2006) ("[E]xamples are not necessary to support the adequacy of a written description"). For example, *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1370-71 (Fed. Cir. 2009) upheld a finding of sufficient written description for claim to a mixed culture of two specific microorganisms, despite the fact that the application contained "no working examples that consolidate cells from different strains," much less a specific example that combined the two claimed strains. Instead, the teachings of the specification as a whole supported the claim. *Id.* at 1370-72.

Moreover, written description "is not about whether the patentee has proven to the skilled reader that the invention works"; it is about whether the skilled reader "can recognize that what was claimed corresponds to what was described." *Alcon*, 745 F.3d at 1191. The Federal Circuit has therefore dismissed as ***irrelevant*** arguments—like those in the Petition— that claim that the type and extent of testing was insufficient support a claim to stable compositions. *Id.* ("[Defendant's] argument regarding the difference between physical and chemical stability, even if correct, is thus not relevant to the inquiry.").

Accordingly, even if Petitioners' construction of "stable" were correct (and it is not), the law would not require the specification to include experimental data demonstrating loss of less than 5% biological activity following two years of storage. *See id.* It is more than enough that the specification presents data which a

POSA would understand shows the claimed stability. *Id.*; *Nuvo Pharms.*, 923 F.3d at 1382 (noting that where the specification included "accelerated stability testing data showing the claimed effect … it was not necessary for the patentee to demonstrate or otherwise 'prove' beyond the data disclosed in the specification that the invention works.").

Nor is Petitioners' call for specific stability data supported by Patent Owner's statements distinguishing the prior art during prosecution. Pet. 22. During prosecution, Patent Owner distinguished Lam, which does not relate to adalimumab, and Salfeld, which does not "provide any specific examples of an adalimumab formulation, and instead provides a general description of pharmaceutical formulations." Ex. 1005, 193-94. Petitioners fail to explain how Patent Owner's statements regarding the unpredictability of arriving at the claimed invention from Lam and Salfeld rise to the level of admissions pertaining to the disclosures of the '581 provisional or the '039 patent. Neither Lam nor Salfeld discloses any specific formulations containing adalimumab at all, let alone stability test data. *See id*. In sharp contrast to those references, the '581 and '039 specifications provide extensive experimental test results and conclusions from PLS analysis of adalimumab formulations, which easily demonstrate that the inventors were in possession of the invention claimed in the '039 patent.

c. Petitioners' Declaration Testimony is Fatally Flawed

Dr. Schöneich's declaration is fatally flawed because it fails to address the extensive disclosure of conclusions from PLS analysis of the stability data reported in the '581 provisional. Other than noting that the PLS modeling indicated that citrate and phosphate buffers were destabilizing, Ex. 1002 ¶ 59, Dr. Schöneich never mentions the inventors' PLS analysis. Instead, Dr. Schöneich's analysis of the '581 provisional focuses almost entirely on whether the inventors disclosed, in a single example that was subjected to stability testing, every element of the claimed formulation. Ex. 1002 ¶¶ 118-120, 123-125, 131-133, 139. Dr. Schöneich fails to acknowledge that the '581 provisional reports the results of a systematic analysis of various adalimumab formulation components, rather than simply reporting preferred formulations.

A POSA, however, would understand PLS analysis, and would recognize that *after* systematically testing the seventy specific formulations described in the '581 provisional, the inventors performed a multivariate analysis of the results that correlated the presence or absence of various components with stability. *See* Section III *supra*. Thus, the inventors *identified structural features* of stable formulations. Dr. Schöneich completely misses this point. *See* Ex. 1002 ¶ 131 n.4 (suggesting the "'common structural features' test" is "immaterial" because the applications do not disclose "a formulation" that includes every claimed element).

By ignoring the inventors' *express conclusions* drawn from the testing, Dr. Schöneich fails to appropriately evaluate how a skilled reader would understand the disclosure of the '581 provisional.

Additionally, Dr. Schöneich's opinions are based on an incorrect viewpoint of a person looking to meet the FDA's stability testing requirements to secure approval of a new drug formulation. *See* Ex. 1002 ¶¶ 78, 94-106, 160. The FDA's drug approval requirements, however, are not the standard for written description or enablement of a patent claim. *See Helsinn Healthcare S.A. v. Teva Pharms. USA, Inc.*, 855 F.3d 1356, 1372 (Fed. Cir. 2017), *aff'd*, 139 S. Ct. 628 (2019) ("Our cases distinguish between the standard required to show that a particular invention would work for its intended purpose and the standard that governs FDA approval of new drugs, including the various stages of clinical trials."); *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994) ("Testing for full safety and effectiveness … is more properly left to the [FDA].").

Similarly, Dr. Schöneich focuses much of his criticism of the '581 provisional's disclosures on the absence of "long-term" stability data or tests that directly measure "biological activity." Ex. 1002 ¶¶ 139-142, 147; *see also* Pet. 35 (arguing that the voluminous stability testing in the '581 provisional is inadequate because it "did not assess the magnitude of any decrease in *biological activity* after storage, and did not measure stability during *long-term storage*…") (emphasis

added). These arguments are irrelevant as a matter of law, because written description does not require "proof" that the invention works. *See Alcon*, 745 F.3d at 1191. These arguments also are premised on an incorrect construction of the term "stable." *See* Section IV.A. *supra*. A POSA would understand that at least the accelerated stability testing described throughout the specification is sufficient to demonstrate that a formulation is "stable" within the meaning of the claims. *Id.*

Moreover, even if "long-term" stability or "biological activity" were required by the claims (and it is not), Dr. Schöneich does not credibly argue that a POSA would have failed to see the correlation between the accelerated stability testing reported in the '581 provisional and these properties. Dr. Schöneich admits that "[a]ccelerated stability testing is thus a useful guide in developing stable formulations." Ex. 1002 ¶ 106; *see also* ¶ 104 (quoting Ex. 1046, 7-8). He further admits that accelerated stability testing is routinely used to "provide a rough assessment of *relative stability versus a standard formulation*." *Id.* ¶ 102 (emphasis added). Dr. Schöneich, however, improperly ignores that the '581 provisional reports stability for various experimental formulations *compared to the standard Humira® formulation*—which was known to exhibit acceptable long-term stability during refrigerated storage, including retaining its effectiveness as a pharmaceutical (*i.e.*, its biological activity). Ex. 2001, 473; Ex. 2002 ¶ 97; *see* Section V.B.1.a *supra*.

A POSA also would have understood that the stability testing methods used in the '581 provisional, including determination of monomer content by SEC, are an appropriate measure of decreasing biological activity over time caused by aggregation and fragmentation relative to the starting adalimumab content. *See* Ex. 1008, 11:4-5 ("*activity* of adalimumab can be lost or decreased due to aggregation and/or degradation") (emphasis added), 13:11-12, 27:24-25. Dr. Schöneich himself repeatedly acknowledges the correlation between biological activity and the aggregation/fragmentation measured by SEC. Ex. 1002 ¶¶ 109, 161. Moreover, the '581 provisional expressly teaches that "bioactivity can be measured by any number of well-known assays including by SEC, dSEC, HIC…" Ex. 1008, 13:11-12. Accordingly, a POSA reading the '581 provisional would understand that the SEC data reported in the specification are an appropriate measure of whether the formulations maintain biological activity during storage.

In sum, a POSA reading the '581 provisional would have understood that the inventors possessed stable formulations of adalimumab as claimed in the '039 patent. By ignoring the inventors' express conclusions and teachings in favor of a search for a specific working example whose biological activity was tested after two years of storage, Dr. Schöneich's declaration fails to credibly support Petitioners' position.

2. The '581 Provisional Describes the Formulations of Claims 5-12, including Sucrose.

Petitioners argue unpersuasively that the '581 provisional lacks "clear guidance that would direct a POSA to combine sucrose in a formulation containing the other elements of claims 5-12." Pet. 31. The '581 provisional expressly states that "the compositions of the invention may also comprise a sugar" and "preferably, the sugar is sucrose or trehalose." Ex. 1008, 14:22-23. Further, original claim 12 recites a formulation comprising a "sugar … selected from the group consisting of sucrose and trehalose." *Id.* at 39. This claim depends from claims requiring a "stable aqueous pharmaceutical composition comprising adalimumab and a single buffer" (claim1); "a pH of about 5 to about 6" (claim 3); and "polysorbate 80" (claim 6). These teachings clearly direct a POSA to include sucrose in the claimed formulations comprising a buffer (including acetate buffer) and polysorbate 80 at a pH of about 5 to about 6. And, as explained above, the conclusions from the PLS testing reported in the '581 provisional clearly support the exclusion of mannitol, citrate/phosphate buffers, and NaCl in stable adalimumab formulations.

The conclusory testimony of Dr. Schöneich stating that a POSA "would not have understood from the general reference to sucrose that the inventors possessed a composition that met all requirements of claims 5-12," Ex. 1002 ¶ 132, is

unpersuasive because it is contrary to the express statements in the '581 specification teaching to include sucrose. Likewise, Dr. Schöneich gives no explanation for his assertion that a POSA would fail to understand—in view of the '581 provisional's express teachings to use "sucrose or trehalose"—that sucrose could be substituted for trehalose in a formulation containing the other elements of the claims (*e.g.*, formulation 42). *See* Ex. 1002 ¶132; Ex. 1008, 14:22-23.

The Federal Circuit's predecessor court has warned against Petitioners' approach here, noting that if a patentee were limited "to claims involving the specific materials disclosed in the examples, … a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently-issued patent to find a substitute." *In re Goffe*, 542 F.2d 564, 566-67 (CCPA 1976). That is exactly the case here. The '581 provisional expressly teaches sucrose as a suitable component of a stable adalimumab formulation; Patent Owner is entitled to claims that cover it.

Moreover, Petitioners and Dr. Schöneich fail to address the knowledge in the art of stable adalimumab formulations comprising sucrose. *See Ajinomoto*, 932 F.3d at 1359 (quoting *Ariad*, 598 F.3d at 1351) (holding written description inquiry should consider, *inter alia*, "the existing knowledge in the particular field, the extent and content of the prior art, [and] the maturity of the science or technology"); *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005) (written

description does not "require a re-description of what was already known"); *Falko-Gunter Falkner*, 448 F.3d at 1367-68. A POSA would not have believed that sucrose would be incompatible with stable adalimumab formulations. *See* Ex. 2005, 45:12-16 (teaching sucrose as a suitable tonicity modifier for adalimumab formulations). Specifically, stable buffer-free formulations comprising adalimumab (at both 50 mg/mL and 200 mg/mL) and sucrose had been published. *Id.* at 140:10-145:6 (Example 22, testing formulations comprising adalimumab and sucrose, and reporting "there was overall stability of the protein in all formulations tested" following 1 month storage at 2-8°C, 25°C, and 40°C). Given this knowledge in the art and the teachings in the '581 provisional, a POSA would not have doubted that the inventors possessed stable adalimumab formulations comprising sucrose and the other claimed components.

Finally, as discussed with respect to "stable" formulations above, Petitioners and Dr. Schöneich fail to acknowledge the inventors' stated conclusions based on the stability tests performed on dozens of adalimumab formulations. Relevant here, the '581 provisional concludes that "mannitol and sodium chloride are destabilizers," Ex. 1008, 13:2, 37:26, and that the sugar trehalose is a "better stabilizer than mannitol," *id.* at 28:5-8. Sucrose is expressly taught as an alternative to trehalose. *Id.* at 14:22-23, 39 (claim 12). A POSA reading the '581 provisional would have understood that the inventors possessed the invention of

replacing mannitol and NaCl (which are the stabilizers / tonicity modifiers in the Humira® formulation), with the sugars trehalose or sucrose, to adjust tonicity and improve stability. The '581 provisional teaches sucrose as an alternative tonicity modifier to NaCl and polyols. *Id.* at 15:23-16:7. Petitioners' sole focus on the formulations "actually tested" is not how a POSA would read the specification, and is contrary to law. *See Alcon*, 745 F.3d at 1190-91; *In re Goffe*, 542 F.2d at 566-67.

3. The '581 Provisional Describes the Formulations of Claims 9-12, including Acetate Buffer and a pH of About 5 to About 6.

Petitioners' argument that the '581 provisional does not teach formulations comprising the acetate-buffered formulations of claims 9-12 is not supported by substantial evidence. Petitioners and Dr. Schöneich again focus entirely on whether a formulation containing every element of the claims was "actually tested," while ignoring the conclusions that the inventors expressly teach based on the results of their stability testing. As explained in Sections V.B.1.b-c above, this approach is incorrect as a matter of law, and does not reflect how a POSA would read the specification.

The '581 provisional teaches multiple formulations of adalimumab comprising acetate buffer, which were used in an experiment "to determine the effect of pH on stability of adalimumab compositions." Ex. 1008, 32 (Example 2,

Table 2A). At a minimum, the '581 provisional teaches that "[a]ll of the samples at pH 3.5 used acetate buffer."[3] Ex. 1008, 32:16-18. The inventors conclude from the Example 2 testing that "formulations at pH 5.2 are much more stable than formulations at pH 3.5." *Id.* at 33. The '581 provisional never states or suggests that acetate buffer is destabilizing or that it should be avoided. *See id.* Rather, the '581 provisional concludes that *pH 3.5* is destabilizing. *Id.*

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[3] Petitioners lack sufficient evidentiary basis for their allegation that the formulations containing acetate buffer in Table 2A were *only* at pH 3.5. The '581 provisional states that "all of the samples at pH 3.5 used acetate buffer"; it does not state that acetate buffer was *not* used in the other samples. Ex. 1008, 32:17-18. To the contrary, the '581 provisional indicates that acetate buffer is implied where a buffer is not expressly stated in Table 2A, because the purpose of Example 2 is to study the effect of pH, not the presence or identity of the buffer. *Id.* at 32:3-5; *see also* Ex. 1001, 38:34-39:55 (presenting tables identical to Tables 2A and 2B of the '581 provisional, and confirming that "[i]f a buffer is not specified, acetate buffer (10 mM) was employed (Table E).") Thus, Petitioners' allegation that acetate buffer was not used in the formulations at pH 5.2 is not supported by any evidence.

A POSA reading the specification thus would have understood that the inventors possessed acetate formulations at the "much more stable" pH of 5.2. *Id.* A working example demonstrating testing data for such a formulation is not required for written description. *See Alcon*, 745 F.3d at 1190-91; *Martek Biosciences*, 579 F.3d at 1371.

Moreover, Petitioners fail to address the fact that it was very well known in the art that acetate buffer is appropriate for use at a pH of about 5.2. For example, a prior adalimumab formulation patent cited in the '581 provisional states:

> The buffer of this invention … most preferably has *a pH in the range from about 5.0 to about 6.5. Examples of buffers that will control the pH in this range include* ***acetate*** (e.g. sodium acetate), succinate (such as sodium succinate), gluconate, histidine, citrate and other organic acid buffers.

Ex. 2004, 8:18-22 (emphasis added); *see* Ex.1008, 12:24-25 (distinguishing formulations described in U.S. 8,261,583). The '581 provisional need not expressly point out that acetate buffer is also useful at pH about 5 to about 6 for a POSA to understand that the inventors possessed the use of acetate buffer at this pH, particularly in view of the '581 provisional's repeated teachings to use a pH of about 5.2 to improve the stability of adalimumab. *See Falko-Gunter Falkner*, 448 F.3d at 1367-68 (holding written description does not require repetition of what is known in the art).

C. The '581 Provisional Enables Claims 1-12, and Petitioners Fail to Satisfy Their Burden to Prove Otherwise

Petitioners fail to meet their burden of demonstrating a lack of enablement. "[I]t is imperative when attempting to prove lack of enablement to show that one of ordinary skill in the art would be unable to [practice] the claimed invention without undue experimentation." *Alcon*, 745 F.3d at 1188 (quoting *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998)) (alterations in original). Petitioners do not substantiate their allegation that a POSA could not practice the claims without undue experimentation; it is contradicted by their own declarant's prior testimony. Petitioners' analysis of the *Wands* factors is perfunctory and completely fails to address critical factors such as the extensive guidance in the specification and the state of the art at the time of the invention.

1. Petitioners Fail to Show That Undue Experimentation Is Required to Practice the Claimed Invention

Petitioners fail to show that undue experimentation would be required to make and use any formulation claimed in the '039 patent based on the teachings in the '581 provisional. Petitioners do not seriously dispute that the specification of the '581 provisional discloses a specific formulation that meets every element of claims 1-4, including the specific concentration of each component. Ex. 1008, 28-29 (Table 1F, formulation 42); Pet. 30, 35, 58; Ex. 1002 ¶¶ 138, 185. This formulation displays stability comparable to the Humira® formulation under

accelerated stability conditions. Ex. 1008, 29 (*compare* formulation 31 (Humira®) *with* formulation 42). Petitioners fail to carry their burden to show that this example does not display the claimed stability, or that any undue experimentation would be required to practice it. *See Alcon*, 745 F.3d at 1189-90.

Little, if any, experimentation would have been needed to prepare an adalimumab formulation comprising acetate buffer and sucrose based on the teachings in the '581 provisional. The specification describes a wide variety of formulations that display stability comparable to Humira®, including the concentration of each component. As noted above, *all* of the formulations tested at pH 5.2 displayed stability similar to or better than Humira® based on SEC following storage under accelerated conditions. *See, e.g.*, Ex. 1008, 28-29 (Table 1F), 32-33 (Table 2B). The '581 provisional teaches that the stability of these adalimumab formulations is improved by 1) using a buffer other than the citrate/phosphate combination; 2) removing NaCl as a tonicity modifier, 3) removing mannitol, 4) including polysorbate 80, and 5) using a pH of about 5.2. *Id.* at 12:20-13:3, 28:6-8, 33. The '581 provisional also expressly teaches the use of acetate buffer, *id.* at 32:17-18, and sucrose (*e.g.*, as a tonicity modifier), *id.* at 3:28-29, 14:22-23,16:4-7. Petitioners do not credibly argue that undue experimentation would have been required to implement these recommendations.

To the contrary, Petitioners' expert, Dr. Schöneich, has testified in other proceedings that only routine experimentation is required to make antibody formulations and test their stability. In an IPR involving an antibody formulation as of 2003 (nearly a decade earlier than the provisionals at issue here), Dr. Schöneich testified that "[a]djusting the various concentrations of the active and inactive ingredients as well as other parameters, such as the pH, to maximize the stability of the formulation would have been ***nothing more than routine optimization*** well within the technical knowledge of a person of ordinary skill in the art." Ex. 2002 ¶ 17 (emphasis added). He elaborated that "standard tests were well known to optimize the stability and solubility based on pH … and surfactant concentration …. Thus, recognizing the necessary stability would be accomplished through standard stability tests also known in the art." *Id.* ¶ 131; *see also* ¶ 61 (admitting SEC is a "well-known stability test"); ¶ 128 ("[S]tandard stability tests used to determine that a formulation will remain stable for the required period of time were well-known prior to February 10, 2003.").

The testimony above belies Dr. Schöneich's contrary statements here claiming that a POSA "would have had to engage in 'undue' experimentation to achieve a 'stable' formulation of adalimumab containing acetate buffer, with or without sucrose, and the claimed pH range." Ex. 1002 ¶148. In particular, Dr. Schöneich's prior testimony that adjusting concentrations of formulation

components requires "nothing more than routine optimization," Ex. 2002 ¶17, is contrary to his opinion here that an alleged lack of guidance as to the "various concentrations of adalimumab, acetate buffer, polysorbate 80 and sucrose" to be combined means that "experimentation [that] goes beyond typical optimization of a formulation" is required, Ex. 1002 ¶¶ 151-152. Routine experimentation is not "undue." *PPG Indus. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996) ("A considerable amount of experimentation is permissible, if it is merely routine."); *Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1338-39 (Fed. Cir. 2013).

Moreover, as explained in Section V.C.3 below, the '581 provisional provides extensive guidance as to the concentrations of each component that would result in stable adalimumab formulations. Petitioners have not presented any evidence that undue experimentation with the concentrations of the formulation components would have been required for a POSA to practice the claimed invention. *See Alcon*, 745 F.3d at 1189 (holding that variables related to *optimizing* the stability of a given formulation are not relevant to whether a POSA could *practice* the claimed invention). The burden is on Petitioners to show that the specification is not enabling; it is "irrelevant here, as a legal matter" whether the specification "contain[s] data proving" that the disclosed formulations display the claimed stability. *Id.* at 1189-90.

Dr. Schöneich's argument that testing adalimumab formulations for stability would be "laborious, time-consuming and iterative" is both incorrect and irrelevant. Ex. 1002 ¶ 153; *Cephalon*, 707 F.3d at 1339 ("Unsubstantiated statements indicating that experimentation would be 'difficult' and 'complicated' are not sufficient" to show that the "experimentation would be undue."). As evidenced by the '581 provisional itself as well as the state of the art, stability testing is not done in a sequential, linear fashion. Parallel experimentation is the norm, and the stability of multiple formulations can be determined concurrently. *See, e.g.*, Ex. 1008 (stability testing formulations in sets of 12); Ex. 2005, 140:10-145:18 (Example 22, reporting stability testing of 16 adalimumab formulations; Ex. 2006 ¶¶ 280-288 (Examples 7 and 8, reporting stability testing 11 adalimumab formulations).

Dr. Schöneich's prior testimony again belies his claims here. Ex. 2002 ¶ 174 (noting that by 2003, various aqueous IgG antibody pharmaceutical formulations had been FDA approved, and there was "less trial and- error and more rational design" involved in developing such formulations), ¶ 17 ("adjusting the various concentrations … to maximize the stability of the formulation would have been nothing more than routine optimization"). Even in this case, Dr. Schöneich admits that "[d]uring pre-formulation and formulation development, when formulators want to generate stability data more quickly to help them know

whether they are on the right track with, e.g., their trial-and-error testing, formulators will use 'accelerated' stability testing." Ex. 1002 ¶ 102. There is no evidence that confirming the stability of formulations within the scope of the claims would require undue experimentation.

2. Petitioners Exaggerate the Breadth of the Claims

Petitioners exaggerate the breadth of the claims in their attempt to manufacture an argument regarding enablement. A POSA would not understand the claimed "buffer" to mean *any* substance with *any* buffering capacity. *See* Section IV.B *supra*. Rather, as Dr. Schöneich has previously testified, by 2003 "it was widely known that there were only a few buffers suitable for the 5-7 pH range for most protein formulations." Ex. 2002 ¶ 43. Seven are taught in the '581 provisional. Ex. 1008, 13:24-25, 32:17-18. Similarly, a POSA would not understand "pH of about 5 to about 6" to mean "pH 4 to 7." *See* Section IV.D. *supra*.

The claims further specify that the composition comprises polysorbate 80 and a sugar or sucrose. Pharmaceutically acceptable sugars were known in the art, and are taught in the specification. *See* Ex. 1001, 9:1-3; Ex. 1008, 14:22-23 ("Preferably, the sugar is sucrose or trehalose"); Section V.B.2 *supra*. Neither Petitioners nor Dr. Schöneich adequately supports—much less provides any

calculations to explain—their allegations that the claims "encompass literally millions of specific compositions." Pet. 40; Ex. 1002 ¶¶ 134, 149.

3. The '581 Provisional Provides Extensive Working Examples and Guidance for Preparing Stable Adalimumab Formulations

Petitioners' allegation that the '581 provisional contains "no working examples" ignores the nearly seventy formulations prepared and tested for stability in the '581 provisional, including formulation 42, which Petitioners admit is within the scope of the claims. Pet. 35, 43. Petitioners disregard these working examples and the PLS analysis and conclusions expressly reported in the '581 provisional. For example, in arguing that "nothing in the provisional applications teaches how to modify these acetate compositions [at pH 3.5 specifically disclosed in Table 2B] in order to achieve the claimed stability," Pet. 43-44, Petitioners completely ignore the provisional's *conclusion* that "formulations at pH 5.2 are much more stable," and its repeated teachings to formulate at a pH of "about 5 to about 6," preferably about 5.2, Ex. 1008, 13:29-31, 33, 36:26-31. Petitioners fail to show that acetate buffered compositions at pH 5.2 would not be stable. To the contrary, Petitioners point out that an adalimumab formulation consisting of acetate buffer, polysorbate 80, sucrose, and water at pH 5.2 has been FDA approved. Pet. 22 n.4 (citing Ex. 1012 at 20).

Similarly, Dr. Schöneich's conclusory opinions that a POSA "would essentially have to start from scratch to develop a stable formulation falling within claims 5-12," *id.* ¶ 152, or "essentially repeat and extend the work of the inventors," *id.* ¶ 153, are not credible. Dr. Schöneich fails to explain why a POSA would "start from scratch" rather than apply the inventors' teachings, *e.g.*, to use a pH of about 5.2 (Ex. 1008, 33, 36:26-31), adalimumab "at a concentration from about 20 to about 150 mg/ml" (*id.* at 13:21-23), and include 0.1% polysorbate 80 (*id.* at 37:9-11). His opinion also ignores the express teaching that the composition may comprise a sugar, preferably "sucrose or trehalose," (*id.* at 14:22-23). Moreover, Dr. Schöneich ignores the state of the prior art, which taught stable adalimumab formulations comprising sucrose, including suitable concentrations of both components, as discussed below. Ex. 2005, 140-141 (Table 52); Section V.C.4 *infra*.

4. Petitioners Ignore that the State of the Art was Well-Developed for Adalimumab Formulations and Methods for Testing Stability

Petitioners entirely fail to address the state of the art at the time of the invention. This is not surprising, because the state of the art was well-developed and demonstrates that no undue experimentation would be required. It is indisputable that testing adalimumab and other protein formulations for stability

was routinely performed by POSAs. *See, e.g.*, Ex. 1008, 13:4-18, 21:29-23:20; Ex. 2004, 7:8-22; Ex. 2007 ¶ 78; Ex. 2002 ¶ 17.

Petitioners and Dr. Schöneich fail to address the knowledge in the art of stable formulations comprising adalimumab at concentrations as high as 200 mg/ml. Ex. 2005, 140:10-145:18. Specifically, known formulations with 200 mg/ml adalimumab and 80 mg/ml sucrose were reportedly stable following one month storage at 40°C. *Id.* at 145:3-6. In view of this state of the art, Petitioners fail to persuasively argue that undue experimentation would have been required to prepare the claimed stable adalimumab formulations at high concentrations, or with sucrose. Pet. 44.

Petitioners also ignore the fact that acetate buffer was known to be appropriate for use at pH about 5 to about 6, so a POSA would have understood that the '581 provisional's teachings to formulate adalimumab at pH 5.2 clearly applies to acetate buffered formulations. Ex. 2004, 8:18-24; Ex. 2002 ¶ 43 (citing Ex. 2003, 12-13).

5. General Unpredictability of Antibody Stability is Irrelevant in View of the Extensive Guidance in the Specification

Instead of providing a cogent analysis grounded in the *Wands* factors, including the guidance set forth in the '581 provisional and the state and level of skill in the art, Petitioners generally refer to Patent Owner's prosecution statements

regarding the unpredictability *over the prior art* of the experimental data and the inventors' conclusions reported in the '581 provisional. Pet. 41-42. Petitioners' attempt to use the inventors' disclosure against them is improper. *See, e.g.*, *Merck Sharp & Dohme Corp. v. Wyeth LLC*, PGR2017-00016, Paper No. 9, at 8-9 (PTAB Oct. 20, 2017) (rejecting enablement challenge). The '581 provisional teaches the POSA how to prepare more stable adalimumab formulations (*e.g.*, by removing the citrate/phosphate buffer used in Humira®). Ex. 1008, 12:19-13:3. It is irrelevant that the inventors' discoveries could not have been predicted *before* the inventors disclosed them.

Again, Petitioners ignore that the '581 provisional reports *the results of* extensive experimentation, in the form of stability data for various additives in combination with adalimumab (*i.e.*, the "specific protein," which was not tested in the Lam and Salfeld prior art distinguished by Patent Owner). Pet. 41; Ex. 1005, 192. The '581 provisional provides detailed PLS analysis of those results and identifies key structural features of stable adalimumab formulations. These structural features are reflected in the '039 patent claims (*e.g.*, elimination of destabilizing citrate/phosphate buffers, mannitol, and NaCl; use of polysorbate 80 and pH about 5 to about 6, preferably 5.2). *See* Ex. 1008, 12:19-13:3, 36:20-31, 37:9-11.

The extensive experimental data and conclusions in the '581 provisional make this case readily distinguishable from *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1346-49 (Fed. Cir. 2019). In *Enzo*, the specification provided a mere sentence suggesting that "the special [labeled] nucleotides of this invention" could be used as "DNA or RNA probes," and a single example of how to make a labeled nucleotide without any data testing a labeled nucleotide for "hybridizability and detectability" (*i.e.*, functionality as a probe). *Id*. at 1347. Here, the specification provides extensive guidance, backed by empirical test data and PLS analysis, teaching POSAs the structural features of stable adalimumab formulations within the scope of the claims.

Petitioners' claims that undue experimentation would have been required to implement the teachings of the '581 provisional fall flat, particularly in view of their own expert's prior testimony that adjusting the concentrations of formulation components and determining stability requires "nothing more than routine optimization," Ex. 2002 ¶¶ 17, 36, 114, 131.

6. Petitioners Fail to Show that the Wands Factors, Taken Together, Show that the '581 Provisional Does Not Enable Any of Claims 1-12.

The '581 provisional teaches to prepare stable adalimumab formulations by excluding destabilizing components and conditions including citrate and phosphate buffers, mannitol, and sodium chloride, low pH such as pH 3.5, and to include

stabilizing components and conditions including buffers other than the citrate/phosphate combination, polysorbate 80, sugars such as sucrose, and pH of about 5 to about 6, particularly about 5.2. Ex. 1008 at 12:19-14:23. The '581 provisional also teaches techniques for stability testing that were routinely performed by POSAs. *Id.* at 2:26-29, 21:29-23:20.

Additionally, the evidence of record demonstrates that adalimumab formulations were well-known in the art. *See, e.g.*, Ex. 1001, 1:66-67. It is indisputable that testing adalimumab and other protein formulations for stability was routinely performed by POSAs, and the state of the art was such that additional stable adalimumab formulations were known. *See, e.g.*, Ex. 1008, 13:4-18, 21:29-23:20; Ex. 2004, 7:8-22; Ex. 2005, 140:10-145:6. Petitioners fail to show that a POSA could not make any formulation within the scope of the claims without undue experimentation.

Petitioners have failed to satisfy their burden of proving that any of claims 1-12 lack enablement and/or written description in the '581 provisional. As such, Petitioners have failed to demonstrate that any of claims 1-12 of the '039 patent has an effective filing date that is on or after March 16, 2013. The '039 patent is not eligible for post-grant review and the Board should deny the Petition because it does not meet the jurisdictional threshold.

VI. PETITIONERS FAIL TO SHOW IT IS MORE LIKELY THAN NOT THAT AT LEAST ONE OF THE CHALLENGED CLAIMS IS UNPATENTABLE.

As a separate and independent ground for denying institution, Petitioners have failed to show that it is more likely than not that at least one claim is unpatentable on any ground. Petitioners' Grounds 1 and 2 fail for the same reasons that Petitioners fail to demonstrate that the '039 patent is PGR-eligible, and for the additional reasons below. Ground 3 (indefiniteness) fails because it is premised on an unreasonable claim construction that is contradicted by the intrinsic evidence.

The '039 patent adds over 100 pages of disclosure to the already extensive teachings in the '581 provisional. This includes hundreds of additional stability experiments, including making and testing dozens more adalimumab formulations, additional PLS analysis incorporating data from that testing, and sixteen new figures from PLS analysis illustrating how stability is affected by varying pH and concentration of formulation components. These disclosures further support the '039 patent claims. For example, the '039 patent includes express description of: stable acetate buffered formulations at pH 5.2, Ex. 1001, 38:34–42:21, stable buffered high-concentration adalimumab formulations, *id.* at 58:61–63, and teachings to use a sugar or polyol instead of mannitol/NaCl as the tonicity modifier, *id.* at 37:35–38:7. All of these disclosures contradict Petitioners' arguments for lack of written description and lack of enablement.

Petitioners' arguments that the '039 patent does not demonstrate "actual possession of any 'stable' formulation within the claims," Pet. 45, and that the claims are not enabled, are wrong for several independent reasons. *First*, Petitioners rely on an unreasonable claim construction of "stable" that disregards all of the undisputedly "voluminous" stability testing presented in the specification. Pet. 18. *Second*, even if Petitioners' claim construction were correct (and it is not), their arguments requiring direct measurement of biological activity, long-term storage, and/or statistical analysis are incorrect as a matter of law. *Third*, Petitioners fail to address key aspects of the '039 patent disclosure, including the comparisons of stable formulations to the commercially-available Humira® formulation, the inventors' correlation of formulation components with stability based on PLS analysis of the "dozens of additional example formulations and stability tests" added over the '581 provisional (Pet. 47), and the '039 patent's express teachings that sucrose and acetate buffer are suitable components of the inventive stable adalimumab formulations.

A. Ground 1: Petitioners Fail to Satisfy Their Burden of Showing That Claims 1-12 Lack Written Description in the '039 Patent.

1. Petitioners Rely on an Incorrect Construction of "Stable"

Petitioners improperly disregard the extensive stability testing reported in the '039 patent specification, alleging that it does not demonstrate a precise

correlation to a "numeric range" of biological activity or expressly measure activity after two years in storage. Pet. 45, 47-53. Under the correct construction of "stable," these arguments are clearly irrelevant. *See* Section IV.A *supra*. A POSA would understand that at least the assays described in the specification are sufficient to determine that an adalimumab formulation is "stable" within meaning of the claims.

2. Petitioners' Attacks on the Stability Data in the Specification Are Irrelevant as a Matter of Law

Petitioners' arguments that the '039 patent does not show that the inventors possessed the claimed invention rely almost entirely on a meritless attack on the *type of testing* used to demonstrate stability. Pet. 47-53. As discussed in Section V.B.1.b, a patent need not include test results demonstrating stability for every species, and certainly does not specifically require long-term studies and direct biological activity assays as Petitioners argue. *See, e.g.*, *Allergan*, 796 F.3d at 1308. Even if Petitioners' construction of "stable" were correct (and it is not), it is unnecessary for the specification to include empirical testing or "prove" that the invention works so long as there is sufficient basis for the POSA to recognize that what is claimed *corresponds* to what is described. *Alcon*, 745 F.3d at 1191; *Ajinomoto*, 932 F.3d at 1360.

Petitioners' arguments that the stability testing in the '039 patent does not sufficiently show "biological activity" also are unsupported. The intrinsic record demonstrates that the stability tests reported in the '039 patent are an appropriate measure of biological activity. Patent Owner expressly stated that "bioactivity can be measured by any number of well-known assays including by SEC." Ex. 1008, 13:11-12. A POSA would have recognized that a high level of biological activity (>95%) is retained by the inventive formulations using this well-known stability assay. *See* Section VI.A.3.b *infra*.

Moreover, as explained below, Petitioners fail to meaningfully address how a POSA would understand the voluminous stability data and PLS analysis disclosed in the '039 patent.

3. Petitioners Ignore the Extensive Disclosure in the Specification

a. Correlation of Structural Features with Stability

Petitioners fail to satisfy their burden of showing a lack of written description, at least because the '039 patent meets the common structural features test. Pet. 47-50. As noted above, the '039 patent greatly expands on the already sufficient disclosures in the '581 provisional, including by providing further PLS analysis of the effect of various formulation components on stability. The specification clearly correlates the presence and absence of particular components

and conditions with achieving the claimed stability. The '039 patent teaches the following structural features of stable adalimumab formulations:

- Avoid the citrate/phosphate buffer combination in favor of another buffer, including that "***acetate is also a suitable replacement for the citrate phosphate buffer combination***." Ex. 1001, 21:40-47 (emphasis added);
- Include ***polysorbate 80*** as a stabilizer. *Id.* at 5:42-44;
- "[R]emoving NaCl from the formulation … will be beneficial for stability." *Id.* at 38:1-7;
- Formulations with ***a sugar or polyol*** (*e.g.*, sorbitol or trehalose) as the tonicity modifier "***in place of mannitol/NaCl***" demonstrated stability superior to Humira®. *Id.* at 37:25-38:4, cols. 33-34 (Table D-2) (emphasis added);
- "pH should preferably be at 5 or higher for best stability.… [T]he ***optimal pH is near 5.2***." *Id.* at 61:24-25 (emphasis added).

The '039 patent teaches appropriate concentrations of each of the above components, and also provides working examples that demonstrate comparable or superior stability to the commercial Humira® formulation. Undisputedly, formulation D-12 includes the components recited in claims 1-4. Pet. 46; Ex. 1001, cols. 33-34 (Table D-2). It displays stability superior to Humira®. *Id.* at

cols. 33-34, 38:1-7 ("The best stability profile by SEC appears to be for Formulations 10 and 11 [sic: 11 and 12] which contain high concentrations of sorbitol or trehalose in place of mannitol/NaCl (Table D-2)."). The specification expressly points out that degradation would be even lower at refrigerated temperatures (*i.e.*, long term storage conditions): "decreases in the main peak appear to be greater at t1 [40°C] than t2 [25°C], suggesting that degradation at 5°C would be almost imperceptible." *Id.* at 38:20-24.

Petitioners fail to explain why a POSA would doubt that formulations that display *improved stability relative to Humira*® would be stable (including displaying stable activity following long-term storage). *Cf.* Ex. 2002 ¶ 97 (Dr. Schöneich testifying that FDA-approved drugs are expected to "maintain stability over a suitable shelf-life"). Indeed, Petitioners fail to acknowledge *at all* that the commercial Humira® formulation is used as a control in the reported stability experiments, despite express statements to that effect in the '039 patent. Ex. 1001, 22:39-40, 37:18-20 ("Once again, the commercial adalimumab (Humira®) formulation was used as a control…").

The '039 patent also presents stability data for three acetate-buffered formulations at pH 5.2, all of which have improved stability over the Humira® formulation. Ex. 1001, cols. 39-40 (Table E-2) (*compare* formulation 1 (Humira®) *with* formulations 3, 9, and 11); *see also id.* at cols. 55-56 (Block H,

formulations 6 & 9) (stable formulations combining acetate with a second buffer). As to adalimumab concentration, the '039 patent reports that a buffered formulation of 100 mg/ml adalimumab in the absence of mannitol, citrate/phosphate buffer, and NaCl was "quite stable." *Id.* at cols. 55-56 (Table H-2), 58:61-63.

All of these examples demonstrate possession of the claimed invention, because a POSA would understand that the results support the inventors' identification of the claimed structural features of stable adalimumab formulations. *See Ajinomoto*, 932 F.3d at 1360. Even under Petitioners' (incorrect) claim construction, the specification's accelerated stability data comparing favorably to the Humira® formulation indicate to a POSA that the inventors possessed formulations that will show stable biological activity following long-term storage. *See* Ex. 1001, 38:20-24.

b. Voluminous New Stability Data

Petitioners also fail to meaningfully address the voluminous new stability test data for the adalimumab formulations presented in the '039 patent. The new data includes stability testing by cIEF and CE-SDS, freeze/thaw, and agitation experiments, in addition to the SEC and RP-HPLC studies reported in the '581 provisional. Ex. 1001, cols. 25-58. These data consistently demonstrate that the inventors possessed adalimumab formulations with stability comparable to or

better than Humira®. For example, Formula D-12 (which Petitioners admit meets the structural requirements of claims 1-4) consistently shows ***less than 5% degradation*** under the accelerated stability conditions tested. *Id.* at cols. 33-34 (Tables D-2 and D-3, showing less than 3% degradation by SEC and RP-HPLC), 38:17-30 (explaining that cIEF indicated "less than 5% (and probably much less than 5%) is degrading," and "little degradation is seen by CE-SDS … At most 2 to 4% degradation is seen…"). The same is true for other formulations at pH 5.2, including three acetate buffered formulations. *Id.* at cols. 39-40 (Tables E-2 and E3, formulations 3, 9, 11)

Petitioners attack each of the SEC, RP-HPLC, cIEF, and CE-SDS assays individually by arguing that they do not "prove" a specific level of biological activity or definitively demonstrate "long term" stability. Pet. 50-53; Ex. 1002 ¶¶ 111, 113, 115. These arguments rely on an incorrect claim construction and are contrary to law. *See* Sections VI.A.1-2 *supra*. Moreover, Petitioners' expert acknowledges that the various stability tests used in the specification *are correlated* with biological activity and long-term stability. *See* Ex. 1002 ¶ 109 (SEC measures aggregates and fragments, which "usually have less activity"), ¶ 111 (RP-HPLC measures impurities, which "often lead to a decrease in biological activity"), ¶ 106 ("Accelerated stability testing is thus a useful guide in

developing stable formulations…"); Ex. 2002 ¶ 181 (acknowledging that cIEF is a known test for protein stability).

Petitioners also fail to address the freeze/thaw ("F/T") experiments at all, despite the fact that these show two buffered formulations with polysorbate 80, free of mannitol, citrate/phosphate buffer, and NaCl demonstrated "little, if any, losses in purity" upon repeated freeze/thaw cycling. Ex. 1001, 54:52-60; *see* col. 48 (Table G, formulations 4 and 11), cols. 53-54 (Table G-7, reporting monomer content by SEC following 5 F/T cycles). These formulations meet every element of claims 1-8, but for addition of sucrose, which the '039 patent teaches is within the scope of the invention. *Id.* at 3:43-44, 67:43-47, 86:45. Moreover, stability following multiple freeze/thaw cycles is indicative of "long term stability" per Petitioners' claim construction. Pet. 11 (quoting Ex. 1001, 9:25-27).

c. Sucrose

Regarding claims 5-12, Petitioners fail to establish that the specification does not describe formulations comprising sucrose. The '039 patent teaches that the formulations of the invention "may also include a sugar, such as sucrose." Ex. 1001, 3:43-44; *see also* 86:44-45 ("said sugar is selected from the group consisting of sucrose and trehalose"). The '039 patent also teaches that sucrose is a suitable tonicity modifier, *id.* at 67:43-47, and that stability of adalimumab formulations can be improved by removing NaCl as a tonicity modifier, *id.* at 37:35-38:7.

Petitioners fail to address these teachings, and thus fail to demonstrate that a POSA would not have understood that the inventors possessed formulations comprising sucrose in the absence of mannitol and NaCl. *See also* Section V.B.2 *supra*. Petitioners' observation that the specific examples do not include sucrose is not relevant, because the specification specifically contemplates its inclusion. *See ScriptPro LLC v. Innovation Assocs., Inc.*, 833 F.3d 1336, 1341 (Fed. Cir. 2016) (holding that "a specification's focus on one particular embodiment … cannot limit the describe invention where that specification expressly contemplates other embodiments").

d. Acetate Buffer

Regarding claims 9-12, Petitioners fail to establish that the '039 patent does not describe acetate buffer. As detailed above, the '039 patent teaches multiple stable formulations comprising acetate buffer, and expressly states that "acetate is also a suitable replacement for the citrate phosphate buffer combination." Ex. 1001, 21:46-47.

Petitioners rely on one out-of-context statement that acetate was found to be a "strong destabilizer" in one PLS model. Pet. 55. However, Petitioners ignore that other PLS models did not find acetate destabilizing. Ex. 1001, 62:36, 62:56–57 (reporting acetate with a coefficient of –0.053 and stating "stabilizers exhibit negative correlation coefficients"). The single model indicating that acetate was

destabilizing does not detract from the inventors' *express statement* that acetate is "a suitable replacement for the citrate phosphate buffer combination" for use in stable adalimumab formulations. *Id.* at 21:46-47. *See ScriptPro*, 833 F.3d at 1341 (holding that "mere recognition in the specification that an aspect … is 'inconvenient' does not constitute 'disparagement' sufficient to limit the described invention—especially where the same specification expressly that contemplates some embodiments of the described invention incorporate that 'inconvenient' aspect").

For all the reasons stated here and in Section V.B. above, Petitioners have not demonstrated that it is more likely than not that they would prevail in showing that the '039 patent lacks adequate written description support for the subject matter of claims 1-12.

B. Ground 2: Petitioners Fail to Satisfy Their Burden of Showing That Claims 1-12 Lack Enablement in the '039 Patent.

Petitioners' arguments for lack of enablement fail for all the reasons in Section V.C. above, and the following additional reasons. Petitioners' analysis of the *Wands* factors is conclusory. As discussed in Section V.C., Petitioners exaggerate the breadth of the claims, ignore the extensive working examples and additional direction and guidance in the specification, and disregard the knowledge in the prior art regarding adalimumab formulations and pharmaceutical buffers.

Most importantly, Petitioners fail to demonstrate that undue experimentation would be required to practice any formulation within the scope of the claims given the extensive guidance and experimental results in the '039 patent.

The '039 patent provides detailed disclosures of stability testing and conclusions from PLS analysis of stability test results that teach the structural features of stable adalimumab formulations. *See* Section VI.A.3 ***supra.*** Additionally, Dr. Schöneich has previously testified that adjusting the concentrations of various components of antibody formulations and testing for stability involves "nothing more than routine optimization well within the technical knowledge" of a POSA. Ex. 2002 ¶ 17; Section V.C.1 ***supra***. In light of that prior testimony and the extensive teachings in the '039 patent, Petitioners do not credibly argue that a POSA would need to engage in "extensive and laborious trial-and-error experimentation" to practice the claimed invention, nor establish that any such experimentation would be undue. Pet. 60.

Petitioners allege that some formulations could be "hard to stabilize," but they offer no evidence whatsoever that undue experimentation would in fact be required to practice any formulation within the scope of the claims. Pet. 59. The allegedly "difficult formulations" Petitioners identify are purely hypothetical and based on exaggerated claim interpretations. ***Id.*** at 58-59; ***see*** Section V.C.1 ***supra***.

For example, Petitioners do not support their argument that undue experimentation would be required because the claims encompass reducing sugars such as glucose. Petitioners present no evidence that glucose destabilizes adalimumab. Even if Petitioners' argument were credited, Petitioners only establish that POSAs would know not to use reducing sugars like glucose when formulating an antibody. *See* Ex. 1002 ¶ 88 (page 46); *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576–77 (Fed. Cir. 1984) (holding claim not invalid for lack of enablement where a POSA could readily select operative components without undue experimentation).

The '039 patent includes additional test data that belies Petitioners' arguments that any claimed formulations would not be stable, or could not be practiced without undue experimentation. The '039 patent clearly demonstrates that acetate buffered formulations at pH 5.2 exhibit comparable or superior stability to Humira®. Ex. 1001, cols. 39-40 (Block E, formulations 3, 9, 11), cols. 55-56 (Block H, formulations 6 & 9); *see* Section VI.A.3.a *supra*. This contradicts Petitioners' suggestions that acetate-buffered formulations would be hard to stabilize. Pet. 59. The '039 patent also demonstrates stability of a buffered formulation comprising 100 mg/ml adalimumab and polysorbate 80, without mannitol, NaCl, or citrate/phosphate buffers. Ex. 1001, 58:61-63. This rebuts Petitioners' suggestion that the specification does not enable formulations

containing higher concentrations of adalimumab. And, the vast majority of formulations at pH 5.2 "meet the stringent 5% upper end" of Petitioners' asserted "claimed stability range," based on multiple well-accepted stability assays. Pet. 59; *see* Section VI.A.3.b *supra*.

Accordingly, for the reasons above and in Section V.C., Petitioners have not demonstrated that it is more likely than not that they would prevail in showing that any claim of the '039 patent is invalid for lack of enablement.

C. Ground 3: Petitioners Fail to Satisfy Their Burden of Showing That Claims 1-12 Are Indefinite.

Petitioners argue that claims 1-12 are indefinite because the phrase "free of … citrate and phosphate buffers" is ambiguous and that the intrinsic record does not resolve the ambiguity. Pet. 61-64. Petitioners are incorrect. The intrinsic record establishes that the correct construction of this phrase is "free of the combination of citrate and phosphate buffers." *See* Section IV.C. *supra*. The term is not ambiguous, and thus claims 1-12 are not invalid.

A claim is invalid for indefiniteness if the claim, viewed in light of the specification and the prosecution history, fails to inform those skilled in the art about the scope of the invention with reasonable certainty. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 899 (2014). A high threshold for ambiguity exists in order to find indefiniteness. *Id*. (holding that the "certainty which the law

requires in patents is not greater than is reasonable"). With regard to the reasonableness standard, one must consider the language in the context of the circumstances. *In re Packard*, 751 F.3d 1307, 1313 (Fed. Cir. 2014); *Interval Licensing, LLC v. AOL, Inc.*, 766 F.3d 1364, 1371 (Fed. Cir. 2014) (holding claims must be "read in light of the specification and the prosecution history").

The plain language of the claims supports Patent Owner's construction. The claims require a composition that is "free of … citrate ***and*** phosphate buffers"—and thus allow the presence of either citrate buffer or phosphate buffer individually. Petitioners incorrectly suggest that use of the plural term "buffers" indicates that the claim excludes something more than "a 'buffer' made of citrate mixed with phosphate." Pet. 61. The claimed composition, however, excludes the combination of "citrate and phosphate buffers," regardless of whether the citrate and phosphate components were first "mixed" together before adding them to the composition or the two buffers are added separately into the composition. If anything, the plural term "buffers" in the claims reinforces that it is the *combination* of these buffers that is excluded, rather than each buffer individually.

Moreover, when the claims are read in the context of the specification and prosecution history (as they must be), it is clear that Patent Owner's construction is the only reasonable interpretation. Throughout the specification of the '039 patent,

the formulations of the invention are contrasted with prior art adalimumab formulations containing the citrate/phosphate buffer combination. For example:

> The relatively poor performance of the buffer combination of citrate and phosphate is rather unexpected considering the apparent importance attributed to the use of a citrate/phosphate combined buffer in U.S. Pat. No. 8,216,583. To the contrary, we have now found that a phosphate/citrate buffer combination is not an optimal choice for obtaining a stabilized adalimumab formulation, and in fact, an element of our invention is the discovery that this combination should be avoided altogether in favor of other buffer systems.

Ex. 1001, 5:18-27.

Petitioners and Dr. Schöneich refer to specification statements out of context and misleadingly truncate statements to advance their argument that the claim could refer to elimination of citrate or phosphate individually. For example, Petitioners misleadingly quote a short section of a sentence that, when read in full, directly contradicts their argument:

> Further, we rank citrate as the poorest of buffers, and preferably avoid it ***although it is still within the scope of the invention to formulate stable formulations of adalimumab that include citrate buffer***, if not the combination thereof with phosphate.

Ex. 1001, 15:21-25 (emphasis added); *Cf.* Pet. 63; Ex. 1002 ¶ 59. Similarly, Petitioners misleading truncate the following specification sections:

> ***The poorest stability would occur when these two buffers were used in combination*** and the effect would get worse as the buffer concentrations increase, according to this model (FIG. 13[**1**]). The response surface indicates that the *phosphate and citrate are equally destabilizing*, ***contrary to some earlier observations, but the quantitative nature of these surfaces must be considered with some care*** as they include data from all of the formulations from Blocks B through H.

Id. at 63:8-16 (emphasis added); *Cf.* Pet. 62; Ex. 1002 ¶ 59.

> Thus, the ***citrate-phosphate buffer combination is not effective at stabilizing adalimumab***, contrary to what is taught by the '583 patent. The destabilizing effect of phosphate is about three-fold greater than for citrate according to this model.

Id. at 64:29-33 (emphasis added); *Cf.* Pet. 62; Ex. 1002 ¶ 59.

The remaining statements cited on Petition pages 62-63 relate to experimental results of measuring or modeling relative stabilizing/destabilizing effects. None of these statements, when read in light of the specification and the prosecution history, renders the claims ambiguous.

Indeed, the '039 patent states more than 50 times that it is the combination of citrate and phosphate buffers that is most destabilizing and excluded, and that neither citrate buffer alone nor phosphate buffer alone is excluded. Among the overwhelming number of statements unambiguously informing the POSA that the combination of citrate and phosphate is excluded, are the following:

- "Accordingly, the comparative benefit of selecting phosphate as a buffer in an adalimumab formulation, due to superior stability in the formulation versus the selection of a citrate/phosphate combination constitutes one of the important aspects of our invention." Ex. 1001, 37:31-35
- [E]ither citrate or phosphate provides better stability than the combination used in Humira® (Table D-3). Again, the avoidance of the citrate/phosphate combination represents an important feature of our invention." *Id.* at 38:9-13.
- "[T]he citrate-phosphate combination is inferior to nearly any other buffer system evaluated, hence an important aspect of the present invention is the avoidance of this combined buffer system altogether." *Id.* at 66:35-38.

Petitioners incorrectly argue that the phrase was not addressed during prosecution. Pet. 62. Petitioners admit that the Examiner stated as a reason for allowance that the claimed formulation is free of "citrate/phosphate combination," Pet. 9 (quoting Ex. 1005, 224), but completely ignore this fact in advancing their indefiniteness arguments, Pet. 62-63. The Examiner clearly understood—as would a POSA—that the claims exclude the *combination* of citrate/phosphate buffers. Ex. 1005, 224. Petitioners' failure to provide any explanation for why a POSA would disregard the reasons for allowance confirming this definition, which is

repeated dozens of times throughout the specification, is fatal to their indefiniteness arguments.

Accordingly, Petitioners have not demonstrated that it is more likely than not that they would prevail in showing that the subject matter of claims 1-12 are indefinite for failing to particularly point out and distinctly claim subject matter which the inventors regard as the invention.

VII. CONCLUSION

For the foregoing reasons, Coherus respectfully requests that institution of the Petition be denied.

Respectfully submitted,

Date: December 23, 2019 By: */ Joseph A. Hynds/*

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that I caused to be served a true and correct copy of the foregoing **PATENT OWNER PRELIMINARY RESPONSE** by electronic mail on this day, December 23, 2019 on the Petitioners' address of record as follows:

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the attached Patent Owner's Preliminary Response to Petition for Post-Grant Review of U.S. Patent No. 10,155.039 contains 16,175 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Response exempted by 37 C.F.R. §42.24(b)(1).

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