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.

PGR2019-00064

Patent No. 10,155,039 B2

Title: STABLE AQUEOUS FORMULATIONS OF ADALIMUMAB

PETITION FOR POST-GRANT REVIEW OF U.S. PATENT NO. 10,155,039 B2

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TABLE OF CONTENTS

TABLE OF CONTENTS
(Continued)

Page

TABLE OF CONTENTS
(Continued)

Page

TABLE OF CONTENTS
(Continued)

Page

TABLE OF AUTHORITIES

Page(s)

Cases

PTAB Decisions

Statutes

Regulations

LIST OF EXHIBITS

EXHIBIT NO.	DESCRIPTION
1001	United States Patent No. 10,155,039 B2
1002	Declaration of Christian Schöneich, Ph.D.
1003	United States Patent No. 6,090,382
1004	United States Patent No. 6,171,586
1005	Excerpts of United States Patent No. 10,155,039 B2 File History
1006	United States Patent No. 8,420,081 ("Fraunhofer")
1007	United States Provisional Application No. 61/698,138
1008	United States Provisional Application No. 61/769,581
1009	United States Provisional Application No. 61/770,421
1010	United States Patent Application No. 14/020,733
1011	United States Patent Application No. 15/360,678 (issued as a U.S. patent No. 9,861,695)
1012	*Application Number: 761024Orig1s000, Labeling*, Center for Drug Evaluation and Research (September 2016) ("Amjevita label")
1013	*Curriculum Vitae* of Christian Schöneich, Ph.D.
1014	Wang, W., "Instability, stabilization, and formulation of liquid protein pharmaceuticals," Int J Pharaceutics 185:129-188 (1999) ("Wang 1999")
1015	Manning, M. *et al.,* "Stability of Protein Pharmaceuticals: An Update," Pharm Res. 27(4):544-75 (April 2010) ("Manning 2010")

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1016	Wang, W. *et al*., "Antibody Structure, Instability, and Formulation," J Pharm Sci. 96(1):1-26 (January 2007) ("Wang 2007")
1017	Drugbank, "Adalimumab," available at https://www.drugbank.ca/drugs/DB00051 ("Drugbank")
1018	*Handbook of Therapeutic Antibodies*, ed. by S. Dübel (WILEY-VCH Verlag GmbH & Co.KGaA, Vol. 1, 2007) ("Dübel 2007")
1019	*Compendium of Chemical Terminology, IUPAC Recommendations*, compiled by A. McNaught and A. Wilkinson (Blackwell Science Ltd., 2nd ed, 1997) ("IUPAC 1997")
1020	*Immunobiology* 5, ed. by C. Janeway et al. (Garland Publishing, 2001) ("Janeway 2001")
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1023	Baker, M. *et al.*, "Immunogenicity of protein therapeutics The key causes, consequences and challenges," Self/Nonself 1(4):314-322 (2010) ("Baker 2010")
1024	Brummit, R. *et al.*, "Nonnative Aggregation of an IgG1 Antibody in Acidic Conditions, Part 2: Nucleation and Growth Kinetics with Competing Growth Mechanisms," J Pharm Sci. 100(6):2014-2119 (May 2011) ("Brummit 2011")
1025	Kayser, V. *et al.*, "Evaluation of a Non-Arrhenius Model for Therapeutic Monoclonal Antibody Aggregation," J Pharm Sci 100(7):2526-2542 (July 2011) ("Kayser I 2011")
1026	Mason, B. *et al.*, "Effect of pH and Light on Aggregation and Conformation of an IgG1 mAb," Mol Pharmaceutics 9:774-790 (2012) ("Mason 2012")

EXHIBIT NO.	DESCRIPTION
1027	Kayser, V. *et al*., "Glycosylation influences on the aggregation propensity of therapeutic monoclonal antibodies," Biotechnol. J. 6:34-44 (2011) ("Kayser II 2011")
1028	USP 30/NF 25, "<788> Particulate Matter in Injections," (The U.S. Pharmacopeial Convention, 2007) ("USP 2007, "<788> Particulate Matter in Injections"")
1029	*FDA Guidance, Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions, Annex 3(R1) Test for Particulate Contamination: Subvisible Particles General Chapter Guidance for Industry*, ICH (FDA, September 2017) ("FDA Guidance 2017")
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1031	*McGraw-Hill Dictionary of Scientific and Technical Terms*, (McGraw-Hill, 6th ed, 2003)
1032	Hawe, A. *et al*., "Forced degradation of therapeutic proteins," J. Pharm. Sci. 101:895-913 (2012) ("Hawe 2011")
1033	Parkins, D. and Lashmar, U., "The formulation of biopharmaceutical products," PSIT 3(4) 129-137 (April 2000) ("Parkins 2000")
1034	Kerwin, B., "Polysorbates 20 and 80 Used in the Formulation of Protein Biotherapeutics: Structure and Degradation Pathways," J Pharm Sci. 97(8):2924-2935) (August 2008) ("Kerwin 2008")
1035	Ha, E. *et al.*, "Peroxide Formation in Polysorbate 80 and Protein Stability," J Pharm Sci. 91(10):2252-2264 (May 2002) ("Ha 2002")
1036	*Formulating Poorly Water Soluble Drugs*, ed. by R. Williams *et al.* (Springer, 2012) ("Williams 2012")
1037	Li, S. *et al.*, "Effects of Reducing Sugars on the Chemical Stability of Human Relaxin in the Lyophilized State," J Pharm Sci. 85(8):873-877 (August 1996) ("Li 1996")

EXHIBIT NO.	DESCRIPTION
1038	Banks, D. *et al.*, "The Effect of Sucrose Hydrolysis on the Stability of Protein Therapeutics during Accelerated Formulation Studies," J Pharm Sci. 98(12):4501-4510 (December 2009) ("Banks 2009")
1039	Gadgil, H. *et al.*, "The LC/MS Analysis of Glycation of IgG Molecules in Sucrose Containing Formulations," J Pharm Sci. 96(10):2607-2621 (October 2007) ("Gadgil 2007")
1040	Gekko, K. and Timasheff, S., "Mechanism of Protein Stabilization by Glycerol: Preferential Hydration in Glycerol-Water Mixtures," Biochemistry 20:4667-4676 (1981) ("Gekko 1981")
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1042	Saunders Nursing Drug Handbook 2011, ed. by B. Hodgson and R. Kizior (Elsevier Saunders, 2011) ("Saunders 2011")
1043	Zhou, S. *et al.*, "Biologics Formulation Factors Affecting Metal Leachables from Stainless Steel," AAPS PharmSciTech 12(1):411-421 (March 2011) ("Zhou 2011")
1044	Zhou, S. *et al.*, "' Biotherapeutic Formulation Factors Affecting Metal Leachables from Stainless Steel Studied by Design of Experiments AAPS PharmSciTech 13(1):284-294 (March 2012) ("Zhou 2012")
1045	Carpenter, J. *et al.*, "Rational Design of Stable Lyophilized Protein Formulations: Some Practical Advice," Pharm Res. 14(8):969-975 (1997) ("Carpenter 1997")
1046	*Guideline for Industry, Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*, ICH Q5C Harmonized Tripartite Guideline (FDA, 1996) ("ICH Q5C 1996")

EXHIBIT NO.	DESCRIPTION
1047	USP 35/NF 30, "<1049> Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products," (The U.S. Pharmacopeial Convention, 2011) ("USP 2011")
1048	Wang, W. and Roberts, C., "Non-Arrhenius Protein Aggregation," AAPS J. 15(3) 840-851 (July 2013) ("Wang 2013")
1049	*Guidance for Industry, Q1A(R2) Stability Testing of New Drug Substances and Products*, ICH (FDA, November 2003) ("FDA Q1A(R2) Stability Testing Guidance")
1050	*Stability testing of active pharmaceutical ingredients and finished pharmaceutical products*, *Annex 2*, WHO Technical Report Series, No. 953 (2009) ("WHO Technical Report Series, No. 953, 2009")
1051	Hong, P. *et al.*, "Size-exclusion Chomatography for the Analysis of Protein Biotherapeutics and their Aggregates," J Liquid Chromatography & Related Techs. 34:2923-2950 (2012) ("Hong 2012")
1052	Chennamsetty, N. *et al.*, "Design of therapeutic proteins with enhanced stability," PNAS 106(29):11937-11942 (July 21, 2009) ("Chennamsetty 2009")
1053	*Stedman's Medical Dictionary*, (Lippincott Williams & Wilkins, 28th ed, 2006)

I. SUMMARY OF GROUNDS FOR INSTITUTION AND CANCELLATION

Fresenius Kabi USA, LLC and Fresenius Kabi SwissBioSim GmbH ("Petitioners") request Post-Grant Review ("PGR") of claims 1-12 of U.S. Patent No. 10,155,039 B2 ("the '039 patent") (Ex. 1001).

As shown in this Petition, and supported by the Expert Declaration of Christian Schöneich, Ph.D. (Ex. 1002) and the other exhibits, the challenged claims have an effective filing date no earlier than September 6, 2013 because the earlier-filed priority provisional applications do not adequately disclose or enable them under 35 U.S.C. §112(a), and are thus eligible for PGR.

Petitioner respectfully requests cancellation of the challenged claims on the grounds that the specification of the '039 patent does not adequately describe the claimed stable compositions of adalimumab, or enable a person of ordinary skill in the art to practice their full scope without undue experimentation. The claims are also indefinite under 35 U.S.C. §112(b).

The Board should institute review because there is a reasonable likelihood that Petitioners will prevail with respect to at least one challenged claim. 35 U.S.C. § 314(a). There is no basis to deny institution under § 314(a) or § 325(d) since this is the first petition by the petitioner challenging a claim of the '039 patent.

A more detailed explanation of the reasons for the relief requested is set forth in section VI below.

II. GROUNDS FOR STANDING

In accord with 37 C.F.R. § 42.204(a) and 35 U.S.C. § 321, Petitioners certify that less than 9 months have passed since the December 18, 2018 issue date of the '039 patent and that the '039 patent is available for PGR. As explained in section V below, at least one claim of the '039 patent has an effective filing date later than March 16, 2013. Petitioners also certify that they are not barred or estopped from requesting PGR on the grounds raised in this petition. The required fee set forth in § 42.15(a) has been paid in accord with 37 C.F.R. § 42.103 and the Commissioner is hereby authorized to charge all fees due in connection with this matter to Attorney Deposit Account 506989.

III. MANDATORY NOTICES

A. Real Parties In Interest (37 C.F.R. § 42.8(b)(1))

The real parties in interest are Fresenius Kabi USA, LLC, Fresenius Kabi LLC, Fresenius Kabi SwissBioSim GmbH, Fresenius Kabi AG, Fresenius Kabi Pharmaceuticals Holding, Inc., Fresenius Kabi Deutschland GmbH and Fresenius SE & Co. KGaA.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

The '039 patent is currently the subject of the following litigation: *Coherus BioSciences, Inc,* v. *Amgen Inc.,* C.A. No. 19-139 (RGA) (D. Del. 2019).

C. Identification of Counsel (37 C.F.R. § 42.8(b)(3)) and Service Information (37 C.F.R. § 42.8(b)(4))

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IV. THE '039 PATENT DISCLOSURE

A. The Alleged Invention of the '039 Patent

The '039 patent is entitled "Stable Aqueous Formulations of Adalimumab" and is generally directed to "stable" adalimumab antibody formulations suitable for "long-term storage." Ex. 1001 at 1:6-10; *See* Ex. 1002 ¶¶ 62-71 for a tutorial on antibody structure). The patent notes that while "[v]arious formulations of adalimumab are known in the art," there is "still need for stable liquid formulations

of adalimumab that allow its long term storage without substantial loss in efficacy." Ex. 1001 at 1:66-2:3. As the inventors explain, when aqueous formulations of adalimumab "are stored on a long-term basis, the activity of adalimumab can be lost or decreased due to aggregation and/or degradation." *Id.* at 10:42-46. According to the inventors, "the present invention provides aqueous formulations of adalimumab that allow stable long-term storage of adalimumab, so that [it] is stable over the course of storage either in liquid or frozen states." *Id.* at 10:46-50. The patent defines "stability" in terms of activity of adalimumab. *Id.* at 9:28-33; Ex. 1002 ¶¶ 44-51.

B. The Claims of the '039 Patent

The '039 patent has 12 claims directed to "stable" adalimumab formulations. Independent claim 1 embraces a broad genus of all "stable" and "aqueous" pharmaceutical compositions comprising

(a) adalimumab;

(b) a buffer;

(c) polysorbate 80; and

(d) a sugar,

wherein the composition is free of i) mannitol; ii) citrate and phosphate buffers, and iii) sodium chloride, and wherein the composition has a pH of about 5 to about 6. Ex. 1001 at 87:33-41.

Claims 2 and 3 depend from claim 1 and are almost as broad. Claim 2 limits the compositions of claim 1 to those containing "about 40 mg of adalimumab," are "suitable for administration to a subject as a single dose," and have an osmolality of "about 180 to 420 mOsM," but does not limit the concentration of adalimumab or any other ingredient. *Id.* at 87:42-45. Claim 3 limits the compositions of claim 1 to those "wherein the pH is about 5.2." *Id.* at 88:1-2. Claim 4 depends from claim 3 and combines the limitations of claims 2 and 3. *Id.* at 88:3-6.

Claim 5 is independent. It is identical to claim 1 except that it limits the "sugar" to "sucrose." *Id.* at 88:7-15. Claims 6 and 7 depend from claim 5, and claim 8 depends from claim 7. They are identical to claims 2, 3 and 4, respectively, except that the "sugar" must comprise "sucrose." *Id.* at 88:16-25.

Claim 9 is independent. It is identical to claim 5 except that it limits the "buffer" to comprising "acetate buffer". *Id.* at 88:26-34. Claims 10 and 11 depend from claim 9, and claim 12 depends from claim 11. They are identical to claims 6, 7 and 8, respectively, except that the "buffer" must comprise "acetate buffer." *Id.* at 88:35-44.

C. Relevant Prosecution History

During prosecution, the Examiner rejected claims 1-12 as being obvious over U.S. Patent 6,090,382 ("Salfeld") (Ex. 1003) in light of U.S. Patent 6,171,586 ("Lam") (Ex. 1004). Ex. 1005 at 177. Salfeld taught combinations of adalimumab

and various pharmaceutical excipients. Lam taught formulations of anti-TNF-α antibodies (a class that includes adalimumab) with a two-year shelf life, comprising acetate buffer, surfactant (a class of compound that includes polysorbate 80) and trehalose, and free of NaCl, mannitol and citrate and phosphate buffers in a pH of about 5 to about 6. Ex. 1004 at 28: Table 2 (formula F2), reproduced below.

TABLE 2

Summary of formulation preparation

Formulation		0.2 M buffer (mL)	18% Mannitol (mL)	20% Trehalose (mL)	1M NaCl (mL)	Approx. Water (mL)	pH	final pH	Made up to (mL)
F1	Acet/5	200	—	—	560	3000	5.07	5.07	4000
F2	Acet/5	200		1600		2000	5.17*	5.07	4000
F3	His/6	200	—	—	560	3900	6.03	6.03	4000
F4	His/6	200	889		—	2800	5.85*	6.01	4000
F5	His/6	200	—	1600		2000	5.97	5.97	4000

*Formulation F2 was adjusted with acetic acid buffer made by diluting 286 μL of glacial acetic acid and 200 mL of the 20% trehalose and mixed with Milli-Q water to a final 500 mL. This is 10 mM acetic acid with 8% trehalose. Approximately 250 mL was required to adjust the pH as required. Formulation F4 was adjusted with 0.5 mL of 50% NaOH.

The Examiner reasoned that a POSA would have been motivated to use the anti-TNF-α antibody formulation in Lam, which describes an embodiment encompassed by the '039 patent claims other than it does not describe adalimumab and it does not specify polylsorbate 80—adalimumab was disclosed in Salfeld—because "the addition of acetate, sucrose and polysorbate in the antibody formulation is known to improve stability and reduce aggregates." Ex. 1005 at 178. The

Examiner further reasoned that because of this motivation, "there would have been a reasonable expectation of success in producing the claimed invention." *Id.*

The applicant countered that a POSA "would not have reasonably expected" from the disclosures in Salfeld and Lam that a formulation containing adalimumab, a buffer, polysorbate 80 and a sugar, such as sucrose, that is also free of mannitol, citrate and phosphate buffers and NaCl, and has a pH of about 5 to about 6, "***would be stable***." Ex. 1005 at 192 (emphasis in original). The applicant asserted that, contrary to the Examiner's view, "the formulation of proteins was known to be ***unpredictable***." *Id.* (emphasis added). In support, the applicant cited the following passage in United States Patent No. 8,420,081 ("Fraunhofer") (Ex. 1006) explaining that testing is required before one can know whether a particular formulation is stable:

> Since the stabilizing effects of additives are protein- and concentration-dependent, each additive being considered for use in a pharmaceutical formulation **must be carefully tested to ensure that it does not cause instability or have other negative effects on the chemical or physical make-up of the formulation**. Ingredients used to stabilize the protein **may cause problems with protein stability over time** or with protein stability in changing environments during storage.

Ex. 1005 at 192 (emphasis in original) (citing Fraunhofer at 2:7-15). The applicant also later asserted that due to the unpredictability in formulating proteins, "***extensive experimentation*** was known to be required for formulating a stable protein

composition." *Id.* at 216 (emphasis in original). The applicant emphasized that Lam did not contain any stability test data for formulations containing adalimumab, and that while Salfeld describes formulations of adalimumab, it "does not provide any data regarding the stability of any particular formulation of adalimumab (much less the specific aqueous formulations of adalimumab that are presently claimed)." *Id.* at 217.

The applicant also distinguished Salfeld and Lam (alone or in combination) from the claimed formulations on the ground that neither Salfeld nor Lam disclosed "with any specificity the presently claimed compositions." *Id.* at 193. The applicant argued that Salfeld does not "provide any specific examples of an adalimumab formulation, and instead provides a general description of pharmaceutical formulations." *Id*. Likewise, Lam does not "teach or suggest with any ***specificity*** an aqueous formulation that includes adalimumab, a buffer, polysorbate 80, and a sugar (such as sucrose), where the composition is free of i) mannitol, ii) citrate and phosphate buffers, and iii) sodium chloride, and the composition has a pH of about 5 to about 6." *Id.* at 194 (emphasis added).

In the summary of the interview conducted on August 15, 2018, the applicant asserted that the Examiners "agreed that [the art already of record] and the lack of data for aqueous adalimumab pharmaceutical compositions in Salfeld and Lam

indicate that one skilled in the art would not have reasonably expected that the presently claimed compositions would be stable." *Id.* at 210.

The Examiner allowed claims 1-12, noting that "the most pertinent prior art neither teaches nor suggests any ***stable*** antibody formulations without mannitol, citrate/phosphate combination and NaCl." *Id.* at 224 (emphasis added).

D. Construction of Claim Terms

Claim terms are to be construed in this proceeding "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent," just as they are in district court. 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc). An inventor is free to act as its own lexicographer "by providing an explicit definition in the specification for a claim term." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998). Where an inventor provides express definitions of claim terms with "reasonable clarity, deliberateness, and precision," those definitions control regardless of the plain meaning. *Id.* (quoting *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994)).

Here, as set forth below, the inventors of the '039 patent provided express definitions for some of the key terms in claims 1-12. A POSA would have viewed the express definitions as clear, deliberate, and precise, and would have applied them

when interpreting the claims. Ex. 1002 ¶ 43. For purposes of this proceeding,[1] any term not expressly defined in the '039 patent should be given its ordinary and customary meaning to a POSA as of the effective filing date of the '039 patent.

1. ***"Stable aqueous pharmaceutical composition"***

The term "stable" is expressly defined in the specification as a range, encompassing formulations that do not lose more than 5% to 20% of their activity during long-term storage:

> The term 'stable' with respect to long-term storage is understood to mean that adalimumab contained in the pharmaceutical compositions does not lose more than 20%, or more preferably 15%, or even more preferably 10%, and even most preferably 5% of its activity relative to activity of the composition at the beginning of storage.

Ex. 1001 at 9:28-33; Ex. 1002 ¶ 44-51. A POSA would understand "activity" to refer to the biological activity of the adalimumab contained in the composition. *Id.* ¶ 50.

[1] Petitioner adopts these claim construction positions for purposes of this proceeding only and reserves the right to change or modify its positions in future litigation, for example in response to expert opinions, statements by the Patent Owner, or judicial rulings.

Other portions of the specification confirm that the term "stable" should be construed to refer to the long-term stability in the express definition. Ex. 1002 ¶ 48. At the beginning of the "Summary of the Invention" section, for example, the inventors described "[t]he invention" as providing "***stable*** aqueous formulations comprising adalimumab that allow its ***long term storage***." Ex. 1001 at 2:5-8 (emphasis added). And in the section entitled "Embodiments of the Invention," the inventors described "the present invention" as providing "***stable long-term storage*** of adalimumab." *Id.* at 10:40-50 (emphasis added).

"Long term storage" is also expressly defined in the specification as a range, encompassing storage for three months to two years under specific conditions:

> The term 'long-term storage' . . . is understood to mean that the pharmaceutical composition can be stored for three months or more, for six months or more, and preferably for one year or more, most preferably a minimum stable shelf life of at least two years. Generally speaking, the terms "long term storage" and "long term stability" further include stable storage durations that are at least comparable to or better that the stable shelf typically required for currently available commercial formulations of adalimumab, without losses in stability that would render the formulation unsuitable for its intended pharmaceutical application. Long-term storage is also understood to mean that the pharmaceutical composition is stored either as a liquid at 2-8° C, or is frozen, e.g., at −20° C, or colder. It is also contemplated that the composition can be frozen and thawed more than once.

Id. at 9:12-27; Ex. 1002 ¶¶ 49-51. From these express definitions, a POSA would have understood the term "stable aqueous pharmaceutical composition" to encompass compositions with a range of stabilities. *Id.* ¶ 51. At the less-stable end of the range are aqueous compositions that do not lose more than 20% of their biological activity when stored for three months or more either as a liquid at 2-8° C, or frozen, e.g., at −20° C or colder. *Id.* At the more-stable end of the range are aqueous compositions that not lose more than 5% of their biological activity when stored for a minimum of two years under the same conditions. *Id.*

Although the term "stable" appears in the preamble of the claim, it is limiting. A term in the preamble cannot be ignored if it is material to patentability. *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329-30 (Fed. Cir. 2005). Here, during prosecution, the applicant distinguished the claimed compositions from the prior-art formulations of Salfeld and Lam on the ground that they are "stable," arguing that neither Salfeld nor Lam presented data establishing that their formulations were stable. Ex. 1005 at 217. The Examiner allowed the claims on this basis, finding that the prior art "neither teaches nor suggests any ***stable*** antibody formulations without mannitol, citrate/phosphate combinations and NaCl." *Id.* at 224. Thus, the claim limitation "stable" was key to patentability.

The applicant also repeatedly described ***the invention*** as being "stable." An applicant's repeated descriptions of the invention as including a term recited in the

preamble also weighs in favor of that term being a limitation. *See Proveris Sci. Corp. v. Innovasystems Inc.*, 739 F.3d 1367, 1372-73 (Fed. Cir. 2014); *Poly-America, L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309-10 (Fed. Cir. 2004). Here, the specification describes the problem allegedly solved by the invention as a "need for ***stable*** liquid formulations of adalimumab that allow its long term storage without substantial loss in efficacy." Ex. 1001 at 2:1-3 (emphasis added). It then identifies "***[t]he invention***" as "provid[ing] ***stable*** aqueous formulations comprising adalimumab that allow its long term storage." *Id.* at 2:7-8 (emphasis added). Under the heading "Embodiments of the Invention," the specification explains that when "formulations of adalimumab are stored on a long-term basis," the biological activity of the adalimumab may be "lost or decreased," and that "***the present invention*** provides aqueous formulations of adalimumab that allow ***stable long-term storage*** . . . so that adalimumab is ***stable*** over the course of storage either in liquid or frozen states." *Id.* at 10:40-51 (emphasis added).

2. ***"Buffer"***

The specification also contains an express definition of "buffer": "[a]s used herein, the term buffer . . . is intended to denote buffer components that introduce buffer capacity in the formulation in addition to any buffering capacity offered by the protein itself, hence the term 'buffer,' etc. is not intended to include the protein itself as a self buffering entity." Ex. 1001 at 2:31-37; Ex. 1002 ¶¶ 54-55. Thus, a

POSA would have understood "buffer" to include *any* substance that has *any* buffering capacity, with the exception of the adalimumab included in the formulation. Ex. 1002 ¶¶ 54-55.

3. ***"Citrate and phosphate buffers"***

The specification does not define the phrase "citrate and phosphate buffers." Ex. 1002 ¶¶ 57-59. As explained in section VI.C below, a POSA would have understood that the phrase could reasonably be interpreted in two ways, the first as excluding citrate and phosphate buffers, whether used individually or in combination, and the second as excluding just a buffer made from the combination of citrate and phosphate buffers. Ex. 1002 ¶ 57. This ambiguity renders the claim indefinite.

4. ***"About"***

The specification defines "about" as follows: "'[a]round,' 'about' or 'approximately' shall generally mean within 20%, within 10%, within 5, 4, 3, 2, or 1 percent of a given value or range." Ex. 1001 at 7:25-27; Ex. 1002 ¶ 56. Thus a POSA would have understood the claimed pH value of "about 5.2" to include a range of pH of ±20%, or pH 4.2-6.2. Ex. 1002 ¶ 56. Similarly, the claimed pH range of "about 5 to about 6" includes pH 4 to 7.2. *Id*. ¶ 56.

5. ***"Sugar"***

The specification defines "sugar" as follows: "'sugar' refers to monosaccharides, disaccharides, and polysaccharides. Examples of sugars include,

but are not limited to, sucrose, glucose, dextrose and others." Ex. 1001 at 9:1-3; Ex. 1002 ¶ 52. The specification distinguishes "polyols" from sugars, offering a separate definition: "'polyol' refers to an alcohol containing multiple hydroxyl groups. Examples of polyols include, but are not limited to, mannitol, sorbitol, and others." Ex. 1001 at 9:4-6; Ex. 1002 ¶ 53. A POSA would have understood "sugar alcohol" to be a type of "polyol." Ex. 1002 ¶ 53. A POSA would also have understood that sucrose is a sugar and not a sugar alcohol or other polyol. *Id.* This is consistent with the specification, which describes sucrose as an example of a sugar and not a sugar alcohol or other polyol. Ex. 1001 at 9:1-3.

6. ***"Single dose"***

The specification does not provide an express definition for "single dose." It refers to the term only in an embodiment discussing a "dispenser device [which] can comprise a syringe having a single dose of the liquid formulation ready for injection." Ex. 1001 at 70:30-32; Ex. 1002 ¶ 60. The terms "dose" (80-100 mg/dose; 0.4 mg/kg to 5 mg/kg of adalimumab), "adult dose" (1-500 mg/m^2, or from about 1-200 mg/m^2, or from about 1-40 mg/m^2 or about 5-25 mg/m^2) and "flat dose" (2-500 mg/dose, 2-100 mg/dose or from about 10-80 mg/dose) are given as various ranges of milligram amounts. *Id.* at 69:17-44. Nothing in the specification indicates that "single dose" is limited to a particular volume or concentration. Ex. 1002 ¶ 60. Therefore, a POSA would understand the 40 mg "single dose" of the claims to

encompass both low (e.g., 50 mg/ml) and high (e.g., 200 mg/ml) concentrations of adalimumab. *Id.*

E. The Disclosure In the Specification of the '039 Patent

As noted in the summary of the prosecution history above (section IV.C), the Patent Owner overcame the prior art references Lam and Salfeld by arguing that they did not disclose any data actually demonstrating that the formulations they described would be stable for long term storage. The same deficiency, however, applies to the '039 patent. While the invention and the claims are drawn to adalimumab compositions that are stable during long-term storage, the inventors do not actually describe specific combinations of adalimumab, buffer, sugar and polysorbate 80 that were stable during long-term storage. Instead, the inventors explain that their work consisted of accelerated stability testing, and that their "discovery" was a general showing that some buffers, sugars, polyols and surfactants are better than others at stabilizing aqueous adalimumab. Ex. 1001 at 4:22-43. Moreover, as described in section VI.A.3, the testing methods only included tests that measure chemical degradation, not changes in activity, which the '039 patent uses to define "stability." The inventors make, for example, the following conclusions from the testing data:

(1) "sorbitol and trehalose are discovered to be significantly better stabilizers of adalimumab formulations than mannitol, unless mannitol is used in

concentrations in excess of about 200-300 mM, in which case the three are generally equivalent." Ex. 1001 at 5:5-10.

(2) "arginine and glycine (and combinations) are discovered to be significantly better stabilizers . . . than sodium chloride." *Id.* at 5:10-13.

(3) "the combination of citrate and phosphate is surprisingly significantly poorer . . . than other buffers such as succinate, histidine, phosphate and tartrate." *Id.* at 5:14-18.

From modeling of the short-term data, the inventors also conclude that:

(1) "The model finds that both phosphate and citrate are destabilizing, with the effect of phosphate being statistically significant (Table LI)." *Id.* at 65:41-43.

(2) "Likewise, acetate is a strong destabilizer as is EDTA." *Id.* at 65:43-44.

(3) "Analysis by SEC showed that the formulation with citrate alone performed more poorly than the buffer combination (Table A), indicating that the phosphate was the primary stabilizer in that combination. This was surprising and unexpected, as this pH is outside of the nominal buffering capacity range of phosphate, but well within the buffering range for citrate." *Id.* at 21:31-37.

Beyond these general conclusions, no guidance is given as to which specific combinations and concentrations of adalimumab, sugar, polysorbate 80 and buffer falling within the claims will provide long-term stability. Ex. 1002 ¶ 158.

While the short-term testing in the specification is voluminous, *see* Ex. 1001 at 20:64-67:20 ("Formulation Studies" for Blocks A-H); Ex. 1002 ¶¶ 154, it contains *almost no* disclosure or testing of *formulations like the claimed ones* that have a buffer, a sugar, polysorbate 80 and a pH of about 5-6, and that do not have mannitol or NaCl or citrate and phosphate buffers. Ex. 1002 ¶¶ 154-55. In fact, the specification discloses *only one* specific formulation that arguably[2] falls within any of the claims: "Block D" formulation 12 ("formulation D-12") arguably falls within claim 1, since it has "adalimumab biosimilar," 10 mM phosphate buffer, 0.1% polysorbate 80, 240 mM trehalose sugar and a pH of 5.44, and does not contain mannitol or NaCal. Ex. 1001 at 31 (Table D-1); Ex. 1002 ¶¶ 154-6. And nowhere does the specification specifically describe or test a formulation that falls within claims 5-12. Ex. 1002 ¶ 177.

All of the dozens of other formulations tested in blocks A-H were missing a buffer, sugar or polysorbate 80, contained mannitol, sodium chloride or a combination of citrate and phosphate, or had a pH of 3.5. *Id.* ¶¶ 154-55.

Even if formulation D-12 of Table D-1 contains the ingredients required by claim 1, the short-term testing of chemical degradation reported by the inventors

[2] If "citrate and phosphate" is construed to not be indefinite and exclude the use of phosphate (*see* section VI.C), formulation D-12 lies outside of the claims.

does not answer the question of whether that formulation meets the requirement that it be "stable," which the patent defined in terms of activity. Ex. 1002 ¶¶ 44-51, 159-61. Further, nowhere do the inventors report any tests on formulation D-12 after long-term storage. *Id.* ¶ 160. While the inventors tested formulation D-12 after being stored for one week at 40 °C, and two weeks at 25 °C (Ex. 1001 at 18:65-67), these short-term storage periods are a fraction of the claimed long-term storage period, which ranges from three months to two years, and used different storage temperatures than the claimed 2-8 °C (liquid), or -20 °C or colder (frozen). *Id.*

Moreover, the inventors only assessed whether chemical degradation of the adalimumab in formulation D-12 had occurred. *Id.* ¶ 161. They do not report the biological activity after storage, as required by the claims. *Id.* The inventors' assays included size-exclusion chromatography (SEC), reverse-phase HPLC (RP-HPLC), capillary isoelectric focusing (cIEF), and capillary electrophoresis sodium dodecyl sulfate gel analysis, (CE-SDS). Ex. 1001 at 19:34-20:62. These assays do not measure biological activity, and the specification contains no correlation between their results and the level of biological activity. Ex. 1002 ¶¶ 161, 163. Further, the specification reports no standard error or analysis of whether the assays performed produced statistically significant results. *Id.* ¶¶ 162.

The inventors' short-term stability tests on formulation D-12 and the long-term stability requirement of the claims are thus apples and oranges. Nowhere do

the inventors explain how the results from the accelerated tests measuring chemical degradation correlate with the long-term loss or maintenance of adalimumab activity in the formulation. *Id.* ¶¶ 161-63.

V. THE '039 PATENT IS ELIGIBLE FOR PGR BECAUSE NONE OF THE CLAIMS HAVE AN EFFECTIVE FILING DATE EARLIER THAN SEPTEMBER 6, 2013

The '039 patent is eligible for PGR because (1) it was filed after March 16, 2013; and (2) the provisional applications on which it relies for a filing date earlier than March 16, 2013 do not provide written description or enablement support under 35 U.S.C. § 112(a) for at least one of its claims. *See* 35 U.S.C. § 119(e). Therefore, the earliest priority date the '039 patent can rely on is the filing date of the first utility application it relies on, namely, September 6, 2013.

A. Chain of Priority For the '039 Patent

The application numbers and filing dates the application No. 15/799,851 that issued as the '039 patent relies on are set forth in the table below.

Application No.	Filing Date	Exhibit No.
Provisional App. No. 61/698,138	September 7, 2012	Ex. 1007
Provisional App. No. 61/769,581	February 26, 2013	Ex. 1008
Provisional App. No. 61/770,421	February 28, 2013	Ex. 1009
Application No. 14/020,733, abandoned	September 6, 2013	Ex. 1010
Application No. 15/360,678, issued as a U.S. Patent No. 9,861,695	November 23, 2016	Ex. 1011
Application No. 15/799,851, issued as U.S. Patent No. 10,155,039	October 31, 2017	Ex. 1005

The specification of the ’039 patent is identical to those of the applications No. 14/020,733 and 15/360,678, which include data that is not present in the provisional applications.

B. The Provisional Applications Do Not Adequately Describe The Compositions of Claims 9-12, Which Require Acetate Buffer And A pH of About 5 To About 6

The claims of the ’039 patent may only obtain the benefit of the filing date of the provisional applications if the applications contain a “written description” of the claimed compositions that complies with 35 U.S.C. §112(a). *See* 35 U.S.C. §119(e) (invention must be disclosed in a provisional application “in the manner provided by section 112(a) (other than the requirement to disclose the best mode)” in order to obtain the benefit of its filing date). The “written description” requirement of § 112(a) is met only if the provisional applications demonstrate “with reasonable clarity” to POSAs that the inventors actually possessed the invention as claimed at the time of filing. *Nuvo Pharms. v. Dr. Reddy’s Labs*., 923 F.3d 1368, 1376 (Fed. Cir. 2019). The essence of the requirement is that a patentee, “as part of the bargain with the public,” must provide a description that allows the public to know that an inventor has truly made a claimed invention. *Id.* at 1376-77. Whether or not a disclosure satisfies the written description requirement is a question of fact. *Amgen, Inc. v. Sanofi*, 872 F.3d 1367, 1379 (Fed. Cir. 2017), *cert. denied*, 139 S. Ct. 787 (2019).

As described in Section IV.C above, the Patent Owner themselves admitted that for a prior-art reference to disclose a stable formulation, the prior art must teach the formulation ingredients with specificity, in terms of combinations and concentrations, and demonstrate stability by presenting test data.

Claims 9-12, filed on October 31, 2017, cover aqueous adalimumab formulations that (1) comprise acetate buffer, (2) have pH of about 5 to about 6,[3] and (3) meet the other limitations of the claims.[4] The provisional patent applications do not satisfy the written description requirement for these claims because, as explained below, they do not disclose acetate formulations that have a pH of about 5 to about 6. Thus, the claims cannot rely on the filing dates of the provisional applications.

[3] Claims 11 and 12 require a pH of about 5.2. Ex. 1001 at 88:39-44.

[4] Patent Owner added claims to acetate buffer formulations only after Amgen, Inc. announced FDA approval of Amjevita®, an adalimumab biosimilar product. The product label for Amjevita®, which was published in 2016, states that "[e]ach 0.4 mL of AMJEVITA is formulated with glacial acetic acid (0.24 mg), polysorbate 80 (0.4 mg), sodium hydroxide for pH adjustment, sucrose (36 mg), and Water for Injection, USP, pH 5.2. Exhibit 1012 at 20 (11: Description); *see also* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761024_toc.cfm.

1. *The ’138 Provisional Application Does Not Describe Formulations Containing Acetate Buffer*

The ’138 provisional application (Ex. 1007) does not describe any compositions with acetate buffer. The description of the invention describes formulations comprising “a buffer selected from the group consisting of citrate, phosphate, succinate, histidine, tartrate and maleate, wherein said composition has pH of about 5 to 6, and wherein said buffer does not comprise both of citrate and phosphate,” (Ex. 1007 at 2:21-23, 4:15-9:13), but makes no mention of acetate buffer. None of the three examples contain acetate buffer. Example 1A contains citrate buffer and mannitol, Example 1B contains citrate buffer and glycine, and Example 1C contains citrate buffer and mannitol. Ex. 1007 at 26:15-17 (Table 1A), 27:10-11 (Table 1B), 28:7-8 (Table 1C). Where, as here, a specification wholly fails to describe an element of a claim, it fails § 112(a). *See Nuvo*, 923 F.3d at 1380 (There must be written description establishing that the inventor was in possession of the “claimed invention, including all of the elements and limitations”); *Messagephone, Inc. v. SVI Sys., Inc.,* 243 F.3d 556 (Fed. Cir. 2000) (reversing the district court’s denial of JMOL of invalidity and explaining that “[t]o satisfy the written description requirement, the specification must describe *every element* of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing”) (emphasis added).

While the application mentions that the formulations may include "other buffers," there is no description of them. Ex. 1007 at 20:26. And while "sodium acetate" appears in a long list of "miscellaneous excipients" that "may be present," it is not described as a buffer. *Id.* at 22:5-11. Moreover, a POSA would not have regarded sodium acetate as being the same thing as acetate buffer.[5] Ex. 1002 ¶ 123. A POSA also would not have understood the inventors to be singling out sodium acetate for use in any specific composition. *Id.* Such general disclosures do not convey "with reasonable clarity" that acetate buffer should be used in the specific compositions of claims 9-12, and thus do not meet the requirements of § 112(a). *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996) ("laundry list" of claim elements does not suffice where there are no "blaze marks" directing them to be combined as claimed).

2. *The '421 Provisional Application Also Does Not Describe Formulations Containing Acetate Buffer*

The '421 provisional application (Ex. 1009) also does not describe any compositions containing acetate buffer. Ex. 1002 ¶ 123. As with the '138 application, it describes adalimumab formulations comprising "buffer selected from the group consisting of citrate, phosphate, succinate, histidine, tartrate and maleate."

[5] Acetic acid must be added to sodium acetate to make acetate buffer. Ex. 1002 ¶ 111.

Ex. 1009 at 2:22-24. The examples provide single-buffer formulations with citrate buffer (*id.* at 25 (Table 1); 26 (Table 2); 27 (Table 3)), histidine buffer (*id.* at 27 (Table 4(a)); 28 (Table 4(b) and 4(c)); 30 (Table 5(a)), and succinate buffer (*id.* at 28 (Table 4(d)); 29 (Table 4(e) and 4(f)); 30 (Table 5(b)), but none with acetate buffer. While the '421 application includes the same list of optional "miscellaneous excipients" as the '138 application, (*See* Ex. 1007 at 22:5-11; Ex. 1009 at 20:26-29), this, as explained, does not pass muster as a description of the specific acetate buffer-containing compositions of claims 9-12.

3. ***The '581 Provisional Application Does Not Describe Stable Formulations Containing Acetate Buffer and Having a pH of About 5 to About 6***

The '581 provisional application (Ex. 1008) also does not describe the acetate buffers-containing formulations of claims 9-12. It describes single-buffer formulations of adalimumab made using the same group of six buffers as the '138 and '421 applications. Ex. 1008 at 3:4-5, 13:24-25 (explaining that the "[b]uffers that may be suitable for purposes of the invention include but are not limited to succinate, histidine, citrate, phosphate, tartrate and maleate."). The only mention of acetate buffer in the '581 application appears in Table 2A.[6] While Table 2A does

[6] The '581 application includes the same list of optional "miscellaneous excipients" as the '138 (Ex. 1007 at 22:5-11) and '421 (Ex. 1009 at 20:26-29) applications.

not state that acetate buffer is present, the specification notes that "[a]ll of the samples *at pH 3.5 used acetate buffer*."[7] Ex. 1008 at 32:16-18 (emphasis added).

Table 2A lists ingredients of Formulations 47-58 (a proprietary source of adalimumab was used as an active ingredient). All of the samples at pH 3.5 used acetate buffer.

Table 2A

Form No	pH	Citrate (mM)	Phosphate (mM)	sorbitol (mM)	Gly	Arg	Mannitol (mM)	NaCl (mM)	PS80 (%)
47	5.2	8	18	0	0	0	65	100	0.1
48	3.5	8	18	0	0	0	65	100	0.1
49	5.2	0	0	0	0	0	65	100	0.1
50	3.5	0	0	0	0	0	65	100	0.1
51	3.5	0	0	65	0	0	0	100	0.1
52	3.5	0	0	0	0	130	0	0	0.1
53	3.5	0	0	0	0	130	0	0	0
54	3.5	0	0	0	240	0	0	0	0
55	5.2	0	0	0	240	0	0	0	0
56	3.5	0	0	0	100	100	0	0	0
57	5.2	0	0	0	100	100	0	0	0
58	3.5	0	0	0	150	50	0	0	0

See Ex. 1008 at 16:29-32. It does not disclose the use of acetate buffer for the reasons previously discussed.

[7] For the formulations described in the '581 provisional falling within the pH range of the claims (pH 5.2) no buffer is included in the formulation. Because Table 2A indicates "0" buffer for formulations at pH 5.2 and does not provide further explanation, a person of ordinary skill would reasonably understand that these formulations did not include added buffer or if they included some buffer, the person of ordinary skill cannot interpret which buffer was present. Ex. 1002 ¶ 121.

Formulation 52 is not an embodiment of claims 9-12, however, because it has a pH of 3.5.[8] Further, as the inventors acknowledged, it was not stable: "[a]s Table 2B demonstrates, formulations at pH of 3.5 ***quickly lose their stability***." Ex. 1008 at 33:3-4 (emphasis added); Ex. 1002 ¶ 120. Nothing in Table 2A—or the rest of the specification—indicates that the inventors were in possession of a stable formulation that contained acetate buffer at a pH of about 5 to about 6. Ex. 1002 ¶¶ 120-24. There is also nothing in the specification that conveys with reasonable clarity that acetate buffer at a pH of about 5 to about 6 should be combined with the other elements of the claims. *Id.* Indeed, the fact that the only formulation containing an acetate buffer was not stable would have taught away from its use. *Id.* ¶ 124.

C. The Provisional Applications Do Not Describe With Specificity The Compositions of Claims 5-12, Which Require Sucrose

The provisional applications also fail to meet the written description requirement for claims 5-12, which require that the formulations contain sucrose as the sugar. As explained below, none of the applications describe any specific examples of sucrose-containing formulations that also meet the other limitations of claims 5-12, such as being free of mannitol, sodium chloride, and phosphate and citrate buffers. Thus, claims 5-12 cannot rely on the filing dates of the applications.

[8] It also does not contain sucrose, which is a separate requirement of the claims.

1. *The '138 Provisional Application Does Not Describe the Sucrose Formulations of Claims 5-12*

The '138 provisional application (Ex. 1007) does not describe any adalimumab formulation that has sucrose along with a buffer, polysorbate 80, and a pH of about 5 to about 6, and that does not have mannitol, sodium chloride or citrate and phosphate buffers. Ex. 1002 ¶¶ 125-28. Example 1A contains no sugar or polysorbate 80 and has mannitol. Ex. 1007 at 26 (Table 1A). Example 1B contains no sugar or polysorbate 80. *Id.* at 27 (Table 1B). Example 1C contains no sugar or polysorbate 80 and contains mannitol, a polyol. *Id.* at 28 (Table 1C).

While the application contains a definition of "sugar" that is similar to the one in the '039 patent,[9] and explains that sucrose is an "example" of a sugar, (*id.* at 7:8-10), the '138 provisional application does not describe the use of sugars generally, or sucrose in particular, to stabilize adalimumab. Ex. 1002 ¶ 128. The application certainly does not describe with reasonable clarity that sucrose should be used in the specific formulations of claims 5-12.

While the application generally describes the use of trehalose, a kind of sugar, this was not a clear disclosure of the use of a sugar in the formulations of claims 5-

[9] "The term 'sugar' refers to monosaccharides, disaccharides, and polysaccharides. Examples of sugars include, but are not limited to, sucrose, glucose, dextrose and others." Ex. 1007 at 7:8-10.

12. Ex. 1002 ¶ 128. The application generally describes the use of polyols to stabilize adalimumab, (*see, e.g., id.* at 11:1-4), and the use of sugar alcohol as a preferred polyol (*id.* at 11:13-15). In a description of preferred sugar alcohols, the application states that "the sugar alcohol is selected from the group consisting of mannitol, sorbitol and trehalose." *Id.* at 11:13-15. A POSA would have understood that unlike mannitol and sorbitol, trehalose is a sugar and not a sugar alcohol (or polyol). Ex. 1002 ¶ 128. Despite this apparent error in chemistry in the description, a POSA would have understood the application as a whole to be describing the use of *sugar alcohol and other polyols* in the invention, not *sugar*. *Id*. The inventors' apparent chemistry error regarding trehalose is certainly not a clear description that *sucrose* should be used as the sugar in claims 5-12. *Id.*

2. ***The '421 Provisional Application Does Not Describe The Sucrose Formulations of Claims 5-12***

Like the '138 provisional application, the '421 provisional application does not describe the use of sugar to stabilize adalimumab, and does not describe specific formulations containing sucrose and all of the other limitations of claims 5-12. Ex. 1002 ¶¶ 129-30. Example 1 contains mannitol and no polysorbate 80 or sugar. Ex. 1009 at 25 (Table 1). Example 2 contains no polysorbate 80 or sugar. *Id.* at 26 (Table 2). Example 3 contains mannitol and no sugar or polysorbate 80. *Id.* at 27 (Table 3). The Example 4 formulations contain no sugar. *Id.* at 27 (Table 4(a)); 28

(Table 4(b), 4(c), and 4(d)); 29 (Table 4(e) and 4(f)). The Example 5 formulations also contain no sugar. *Id.* at 30 (Table 5(a) and 5(b)).

The inventors appear to have copied into the '421 application the same apparent chemistry error regarding trehalose that appears in the '138 application. *See id.* at 5:3-8. But again, this confusion over the chemical designation of trehalose does not amount to a clear description of the use of sugar generally, or sucrose in particular, to stabilize adalimumab, nor of the specific sucrose-containing formulations of claims 5-12. Ex. 1002 ¶ 128.

3. *The '581 Provisional Application Does Not Disclose the Sucrose Formulations of Claims 5-12*

Example formulation 42 in the '581 application describes an adalimumab formulation with 10 mM phosphate buffer, 0.1% (w/v) polysorbate 80, and trehalose. *See* Ex. 1008 at 26 (Table 1D). This appears to be the same formulation as D-12 in the '039 patent specification. However, this formulation contains *trehalose, not sucrose*.[10] Ex. 1002 ¶ 131. While the specification states that "the compositions of the invention may also comprise a sugar" and that "preferably the

[10] Formulation 42 (a.k.a. D-12) also uses phosphate buffer. If "citrate and phosphate" is interpreted to mean that phosphate cannot be used in claims 5-12, then formulation 42 falls outside the scope of the claims for this reason as well.

sugar is sucrose or trehalose," (*id.* at 3:27-30), "the compositions of the invention" is a broad term that does not indicate with reasonable clarity or specificity in which specific compositions such substitution can be made. Ex. 1002 ¶ 132-33. The '581 application describes many different "compositions of the invention," many of which contain mannitol, sodium chloride and citrate and phosphate buffers, which are not embodiments of claims 5-12 (*See* Ex. 1008, Claim 2 directed to both phosphate and citrate as alternative buffers). Ex. 1002 ¶¶ 132-33. The application does not describe a specific formulation containing sucrose, and provides no clear guidance that would direct a POSA to combine sucrose in a formulation containing the other elements of claims 5-12. *Id.* Where, as here, a specification discloses many alleged inventions, a general statement that an excipient may be used "in the invention," when unconnected to the invention of the *claims*, does not satisfy § 112(a). *See, e.g., Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349-50 (Fed. Cir. 2013); *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd*., 323 F. Supp. 3d 566, 624-29 (D. Del. 2018).

D. The Provisional Applications Do Not Disclose the "Stable" Formulations of Claims 1-12

Claims 1-12 require the formulations to be "stable." As explained, a POSA would understand "stable" to encompass a range of stabilities: At the less-stable end of the range, a composition may lose up to 20% of its biological activity when stored for three months or more either as a liquid at 2-8° C., or frozen, e.g., at −20° C. or

colder. Ex. 1002 ¶ 51. At the more-stable end, a composition must not lose more than 5% of its biological activity when stored for a minimum of two years under the same conditions. *Id.*

Where, as here, a patentee claims a specific result such as stability, the specification must demonstrate to POSAs that the inventors were in possession of an invention that actually achieves the claimed stability. *See Nuvo*, 923 F.3d at 1381 (holding that where inventor chose to claim the therapeutic effectiveness of both uncoated and coated PPI, and the specification did not demonstrate that uncoated PPI would be effective, the claims were invalid).

Moreover, where, as here, a claim limit spans a range, the specification must demonstrate that the inventors were in possession of an invention that achieves *the full range*. *See Adello Biologics LLC et al. v. Amgen Inc., et al.*, Case PGR2019-00001, Paper No. 13 (PTAB April 19, 2019) (holding claims to "at least about 25% properly refolded proteins" invalid because specification did not disclose any percentage of properly refolded proteins over 80%); *Abbvie*, 759 F.3d at 1301 (written description must "support the full scope of the claims.").

To satisfy §112 (a), the provisional applications must not only demonstrate with reasonable clarity that the inventors were in possession of "stable" formulations, but—given that the term is framed as a range—possession of formulations that achieve, e.g., the upper end of the range. This includes

compositions that lose no more than 5% of their activity after a minimum of two years.

As explained below, the provisional patent applications fall far short of demonstrating possession of any "stable" formulations, never mind those that achieve the more demanding no more than 5% loss of stability upper limit.

1. *The '138 and '421 Provisional Applications Do Not Contain Any Data Demonstrating Stability*

As the Patent Owner asserted during prosecution of the '039 patent, establishing that an antibody formulation is stable requires empirical testing. Ex. 1005 at 216-17; *see* Ex. 1002 at ¶¶ 72-115 for a tutorial on antibody stability. To demonstrate possession of the claimed "stable" compositions, the provisional applications must describe empirical data sufficient to demonstrate that the claimed formulations have the claimed degree of stability. The '138 and '421 applications, however, do not disclose *any* empirical stability data. These applications state only that the compositions of the examples "can be tested" for stability, and the inventors described only a bald "belief" that the compositions "will be" stable. For example in Example 1A of the '138 application, the inventors state:

> It is ***believed*** that the composition will be stable over the term of two years or more without the need for the presence of a surfactant.

Ex. 1007 at 27:4-5 (emphasis added). Similarly, in Example 4 of the '421 application, the inventors explain:

> It is ***believed*** that the composition will be stable over the term of two years or more without the need for the presence of polyol, and without need for a mixed buffer system of citrate and phosphate.

Ex. 1009 at 30:1-3 (emphasis added).

Mere "belief" that a composition will be stable is not sufficient to demonstrate possession. Nor is a disclosure that would give a POSA a "reasonable expectation" of stability. *See Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (Specification that merely rendered claimed subject matter obvious did not to satisfy written description requirement). Nor even a disclosure that shows how to use routine experimentation to make formulations with the claimed level of stability. *Amgen*, 872 F.3d at 1377-78. *Actual possession* must be demonstrated with reasonable clarity. *Nuvo*, 923 F.3d at 1376. Even the Patent Owner acknowledged as much during prosecution. *See* Section IV.C.

Even if one credits the inventors' belief that the examples of the '138 and '421 applications would be stable if tested, those examples have different ingredients than the claimed formulations. Stability will vary from formulation to formulation depending on the ingredients present and their concentrations. Ex. 1002 ¶¶ 5, 95, 143, 156. The stability of formulations with different combinations and concentrations of ingredients does not, absent some correlation or showing of interchangeability of ingredients, that is certainly not present in the '138 or '421 applications, demonstrate that the claimed formulations are stable. *Id.*

2. *The Data in the '581 Provisional Application Do Not Demonstrate the Claimed Stability*

The '581 application discloses empirical stability testing, for example, for formulation 42, which arguably contains ingredients that fall within claim 1.[11] But a POSA would not have regarded the single SEC experiment[12] disclosed for formulation 42 as demonstrating with any reasonable clarity that the formulation achieved the claimed stability. Ex. 1002 ¶ 139. The only conclusion that the inventors drew from the SEC results is that "degradation by both aggregation and fragmentation (i.e., hydrolysis) occurs during storage." Ex. 1008 at 27:24-25. The testing did not assess the magnitude of any decrease in biological activity after storage, and did not measure stability during long-term storage under the claimed conditions. Ex. 1002 ¶ 139. The samples were stored for only one week at 40° C, or for two weeks at room temperature. Ex. 1008 at 27:18-19. These conditions are

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[11] This assumes the term "citrate and phosphate buffers" is construed to permit phosphate. If phosphate is excluded from the claims, formulation 42 is not an embodiment of any of claims 1-12.

[12] The inventors also conducted RP-HPLC testing on formulation 42, but conceded that the test yielded no useful data: "[a]fter mathematical analysis, the current RP HPLC did not appear to be stability-indicating." Ex. 1008 at 27:20-24; Ex. 1002 ¶¶ 140.

far different than the claimed long-term storage, and the inventors disclosed no correlation between the test conditions and the claimed conditions. Ex. 1002 ¶¶ 139-40. The reported data also do not indicate whether the very small differences in reported SEC values before and after testing were statistically significant. *Id.* ¶ 142. A POSA would not have viewed this testing as demonstrating with reasonable clarity that formulation 42 had a stability falling within the claimed range. *Id.* ¶¶ 139-42.

And confirming that an antibody composition actually meets the more stringent 5% stability requirement would have required an even more discriminating test than one capable of verifying stability somewhere within the claimed range. *Id.* ¶ 142. Not only did the inventors not disclose the results of such testing, they did not even disclose a method a POSA could use to generate such results. *Id.* ¶ 139.

Moreover, as discussed, formulation 42 does not contain sucrose or acetate. Given that it contained different ingredients, a POSA would not have viewed stability testing of formulation 42 as demonstrating that the formulations of claims 9-12, which require acetate buffer, or claims 5-12, which require sucrose, meet the claimed level of stability. *Id.* ¶ 131.

3. ***The Provisional Applications Do Not Demonstrate Possession of the Broad Genus of "Stable" Formulations of Claims 1-4***

A POSA would not have viewed the stability testing in the '581 application as demonstrating possession of claims 1-4. Claims 1-4 are broad genus claims

covering millions of different compositions having a range of stabilities. Ex. 1002 ¶¶ 134. Section 112(a) requires that the written description demonstrate possession of the *full scope* of the genus, and not merely some species within the genus. *Amgen*, F.3d at 1373. Two tests have been used to gauge compliance with this requirement: the "representative species" test and the "structural features" test. As the Federal Circuit has explained,

> Demonstrating possession 'requires a precise definition' of the invention. To provide this 'precise definition' for a claim to a genus, a patentee must disclose 'a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus.'

Id. (quoting *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350-51 (Fed. Cir. 2010) (en banc)).

The representative species test does not require disclosure of every species in the genus; however, "merely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species." *Ariad*, 598 F.3d at 1351. A patentee needs to show that it has "conceived and described sufficient representative species encompassing the breadth of the genus." *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).

Here, even if the '581 provisional application demonstrated that formulation 42 had a stability that fell within claims 1-4, one species is not nearly enough to demonstrate that the entire genus of millions of compositions will meet the claimed range of stability. Ex. 1002 ¶¶ 143-45. Stability will vary widely across the genus as ingredients and concentrations vary. *Id.* Many of the embodiments falling within the claims have ingredients that could diminish or destroy stability. *Id.* For example, higher concentrations of antibody, such as adalimumab, can destabilize a formulation. *Id.* ¶ 156. Oxidizing sugars like glucose can degrade the adalimumab. *Id.* If the inventors are to be credited, formulations with acetate will also be difficult to stabilize, since "acetate is a strong destabilizer." Ex. 1001 at 65:43-44. Moreover, combinations of ingredients can behave in ways that may not be predictable from the behaviour of the ingredients by themselves, as the inventors acknowledge with citrate and phosphate. *See id.* at 38:13-16 ("[i]t could not have been known or predicted that citrate alone, or phosphate alone would provide better formulation stability than . . . a combination of citrate and phosphate."); Ex. 1002 ¶ 145.

Given this variability, to describe the scope of the genus and show possession of it under the representative species test, provisional applications had to disclose more than just formulation 42; they had to describe enough examples to show which specific combinations of ingredients and concentrations within the genus are "stable" and thus within the claim, and which are not. They also had to describe at

least one embodiment that met the 5% upper range of stability. Disclosing one questionable example utterly fails the test. *Pernix*, 323 F. Supp. 3d at 628.

Turning to the structural features test, "functional claim language can meet the written description requirement when the art has established a correlation between structure and function" such that disclosure of a particular structure implicitly discloses the claimed function. *See Ariad*, 598 F.3d at 1350. In other words, the provisional applications may satisfy the structural features test if they disclose which ingredients and concentrations within the genus—the "common structure"—correlate with the claimed stability—the "functional" claim limitation of the genus. The provisional applications are devoid of any test data or other information that demonstrate a correlation between the claimed ingredients and the claimed stability. Ex. 1002 ¶ 147. Thus, the provisional applications also do not pass the structural features test.

E. The Provisional Applications Do Not Enable Claims 1-12 of the '039 Patent

In order for claims 1-12 to be entitled to the filing date of the provisional applications, the applications must also enable a POSA to make and use the full scope of the claims without "undue experimentation." *Ariad*, 598 F.3d at 1352. Factors that may be considered in determining whether "undue experimentation" is required to practice a claim includes the "*Wands"* factors:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir 1988). Enablement is a legal question based on underlying factual determinations. *Vasudevan Software, Inc. v. MicroStrategy, Inc.,* 782 F.3d 671, 682 (Fed. Cir. 2015).

An analysis of the *Wands* factors shows that claims 1-12 of the `039 patent are not enabled by the description and examples provided in the provisional applications.

1. ***Claims 1-12 Are Extremely Broad***

Claims 1-12 of the ’039 patent are very broad. The term “buffer” covers *any* substance or *combination* of substances that has *any* buffering capacity other than adalimumab. Ex. 1001 at 2:31-37; Ex. 1002 ¶¶ 54-55. The term “sugar” covers *any* monosaccharide, disaccharide, or polysaccharide and any *combination* of those sugars. Ex. 1001 at 9:1-3; Ex. 1002 ¶¶ 52-53. The term “pH of about 5 to about 6” covers a range stretching ±20%, i.e., pH 4 to 7.2. Ex. 1001 at 7:25-27; Ex. 1002 ¶ 56. The compositions are also unlimited as to the concentration of adalimumab and other ingredients. Ex. 1002 ¶ 60, 134, 149. Thus, the ingredient limitations of the claim encompass literally millions of specific compositions. *Id.* ¶ 134, 149.

The only limitation on this enormous list of possible combinations is the requirement that the formulation be "stable." *Id.* However, as explained above, the '039 patent's definition of stability is a range that is also relatively broad. A POSA would understand that the universe of "stable" formulations is still extremely large. *Id.* ¶ 149.

2. ***Antibody Stability is Unpredictable***

As discussed above, the Patent Owner advocated throughout the prosecution that making stable adalimumab formulations is highly unpredictable and "depends on both the ***specific protein***, as well ***as each additive*** that is present in the formulation." Ex. 1005 at 192 (emphasis in original). This is also evident in the '581 application:

> Figure 3 contains a depiction of the monomer content at t1 (model 1) as a function of citrate and phosphate concentrations. The pH has been fixed at 5.2. The model indicated that phosphate and citrate by themselves were weak destabilizers (not to statistical significance), along with tartrate and maleate. By comparison, succinate, which is structurally similar to citrate, tartrate and maleate, was a weak stabilizer. The only buffer found to be a significant stabilizer was histidine. ***None of these findings could have been predicted based on the literature or examination of the chemical structure of each buffer***.

Ex. 1008 at 29:11-30:2 (emphasis added).

A POSA would also have been aware that the stability of antibody formulations may vary substantially depending, e.g., on the particular ingredients

and concentration of protein present, and that testing is usually required before it can be known whether a particular composition actually meets a particular stability level, such as those within the claimed range. For example, a POSA would have known that high-concentration antibody formulations require typically very different combinations of excipients to stabilize them from lower concentration antibody formulations. A POSA would not have viewed a formulation with 50 mg/ml antibody concentration as establishing that the same formulation with 200 mg/ml will be stable. *Id.* ¶ 150. And the claims are not limited to any specific adalimumab concentration. *Id.* ¶ 60.

Where, as here, the claim scope is broad and it is often difficult to know in advance of testing whether a formulation actually achieves a given stability goal, to enable the claims the specification must provide a more detailed and comprehensive guide as to how to construct formulations with the claimed ingredients so that they achieve the claimed stability. *See Enzo Life Sciences, Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1346-49 (Fed. Cir. 2019) (finding patent invalid for lack of enabling disclosure where "[t]he scope of the claims is quite broad" and "guidance as to how such variables would or would not impact the functionality of the claimed [invention] is sparse."). But as explained, the provisional applications fail to provide such a guide. Ex. 1002 ¶ 151.

3. *The Specification of the Provisional Applications Provides No Working Examples*

As described above, none of the provisional applications disclose a working example of a stable adalimumab formulation that would fall within the scope of any of the claims, other than possibly formulation 42.

4. *The Description of the Provisional Applications Provides No Written Examples*

As described above, none of the provisional applications disclose a specific written example of a stable formulation, other than possibly formulation 42, that would fall within the scope of any of the claims, and even that fails to demonstrate stability in terms of activity. *See* Ex. 1002 ¶¶ 117-133.

5. *The Amount of Guidance in the Provisional Applications Is Limited*

The claims are directed to compositions that meet a specific stability requirement. As described, the provisional applications provide little guidance as to how to make a "stable" adalimumab formulation using the claimed ingredients, other than to engage in trial and error experimentation. Ex. 1002 ¶ 6, 151. For example, the specification states that compositions with acetate buffer and a pH of 3.5 "quickly los[t] their stability,"[13] (Ex. 1008 at 33:4), and yet claims 9-12 are directed

[13] The '039 patent similarly concludes that acetate is a "strong destabilizer." Ex. 1001 at 65:42-43.

to stable acetate comprising compositions. Nothing in the provisional applications teaches how to modify these acetate compositions in order to achieve the claimed stability.

6. *Taken Together, the Wands Factors Show the Provisional Applications Do Not Enable Claims 1-12*

In view of the extraordinarily broad claims, the need for experimental verification of stability, the absence of any demonstration that a formulation with the claimed ingredients actually has the claimed stability, few (or no) examples with the claimed ingredients, statements teaching away from the claimed compositions, no guidance on how to perform long-term stability testing that measures biological activity, and no correlation between the stability data from chemical degradation tests and the claimed level of stability as measured in activity, the disclosures of the provisional applications would require a POSA to engage in undue experimentation to make and use the invention as claimed. *See* Ex. 1002 ¶¶ 148-53. Therefore, the provisional applications do not provide an enabling disclosure to claims 1-12 as is required by 35 U.S.C. §119(e).

VI. THE PRECISE RELIEF REQUESTED FOR EACH CHALLENGED CLAIM AND THE REASONS THEREFOR

A. Ground 1: The Specification Of the '039 Patent Does Not Provide Adequate Written Description Support For Claims 1-12

Claims 1-12 are invalid under 35 U.S.C. § 282(b)(3)(A) because the specification of the '039 patent does not comply with the written description

requirement of 35 U.S.C. § 112(a). The '039 patent specification added little to the disclosures of the provisional patent applications in terms of examples of formulations that falls within the scope of the claims, empirical test data demonstrating that such formulations are "stable" as defined in the patent, or guidance as to which particular combinations of ingredients and concentrations result in "stable" formulations. Ex. 1002 ¶¶ 154-55. The '039 patent specification, like the provisional applications, would not have demonstrated with reasonable clarity to a POSA that the inventors had actual possession of any "stable" formulation of the claims, never mind the full scope of the millions of formulations that fall within the claims.

1. ***The Specification Fails the Representative Species Test for Claim 1***

The '039 patent specification does not pass the "representative species" test any better than the provisional applications. As explained, claim 1 is a broad genus claim and stability must be verified by empirical testing. In fact, the Patent Owner emphasized in the '039 patent specification that combining buffers can produce unpredictable results:

> The model also indicated that when citrate and phosphate buffer are used together, the formulation is least stable. If one only uses a single buffer, especially phosphate, stability improves. This is surprising, as phosphate has little or no buffer capacity at pH 5.2, while citrate buffer

does. *None of this behavior could have been predicted* based on what was known in the art.

Ex. 1001 at 60:12-28. The inventors added little to supplement what was in the provisional applications to address this variability. Ex. 1002 ¶¶ 154. Although the specification discloses dozens of additional test formulations, the only one that may be an embodiment of the claims is formulation D-12, which appears to be formulation 42 from the '581 provisional application with a different label.[14] *Id.* All of the other test formulations added to the specification (a) contain citrate and phosphate, mannitol or sodium chloride, (2) do not contain a sugar or polysorbate 80, or (3) have a pH of about 3.5. *Id.* ¶ 155.

This lone embodiment does not satisfy the representative species test for the '039 patent specification any better than it did for the '581 application. *Id.* ¶ 156. As explained, "[w]hen there is substantial variation within a genus claim, a sufficient variety of species must be described to reflect the variation within the genus." *Adello Biologics*, Case PGR2019-00001, Paper No. 13 (PTAB April 19, 2019) (citing *AbbVie*, 759 F.3d at 1300). Given that claim 1 requires a particular range of stability, and given that stability will vary among species with different ingredients and

[14] Again, if "citrate and phosphate" is construed to not be indefinite and exclude the use of phosphate (*see* section VI.C), then formulation D-12 lies outside of the claims.

concentrations, empirical test data on a single species would not have described with reasonable clarity to a POSA which of the millions of possible species are stable enough to be members of the genus. It also would not have described whether any of the species have stability at the upper end of the claimed range. The '039 patent specification thus does not demonstrate possession of the full scope of the genus under the representative species test.

2. *The Specification Fails the Common Structural Features Test for Claim 1*

The empirical test data added to the '039 patent specification also does not earn a passing grade on the "common structural features" test. Although the specification adds dozens of additional example formulations and stability tests to what was in the provisional applications, it does not correlate particular combinations and concentrations of the claimed ingredients, *i.e.*, common structural characteristics, with achieving the claimed stability, *i.e.*, the functional claim limitation. Ex. 1002 ¶ 158.

For example, additional test data for formulation D-12, a.k.a formulation 42, are reported in the '039 patent specification, in addition to the previously-reported size-exclusion chromatography (SEC) data, the specification reports the results of reverse-phase high-pressure liquid chromatography (RP-HPLC), capillary isoelectric focusing (cIEF) and capillary electrophoresis in sodium dodecyl sulfate gel media (CE-SDS). *See* Ex. 1001 at 20:64-67:20. But each of the additional tests,

like SEC, attempts to quantify chemical degradation products that may form as adalimumab degrades during long-term storage. Ex. 1002 ¶ 161-63. They do not measure biological activity, as the claims require. *Id.* The '039 patent specification also does not correlate the amounts and types of degradation products measured by these assays with any specific level of biological activity, either by referencing scientific literature or disclosing an experiment that establishes a correlation. *Id.* ¶ 182. Absent some disclosure in the specification, a POSA would not have understood whether and how the tests measuring chemical degradation correlate with the numeric range given for the adalimumab activity recited in the definition of the term "stable."

Moreover, as in the '581 provisional application (Ex. 1008), all of the empirical tests were performed on samples stored for only one week at 40° C, and two weeks at 25° C. Ex. 1001 at 18:65-67. The specification does not correlate stability under these brief periods of storage with stability between 3 months and two years under the claimed conditions, either by referencing the scientific literature or disclosing an experiment that establishes a correlation. Ex. 1002 ¶ 141-42. Again, without some correlation disclosed in the specification, a POSA would not have understood how the results from the accelerated test conditions correlate with the claimed long-term storage conditions. *Id.*

The specification also does not correlate the stability of formulation D-12 with the stability of any other species of claim 1. *Id.* ¶ 161. While the specification asserts that PLS modeling of the one- and two-week testing performed on unclaimed formulations demonstrate that certain buffers like citrate-phosphate are "inferior" and others, such as histidine-succinate "offer[] very good stability," (Ex. 1001 at 66:27-67), or that "acetate is a strong destabilizer" (*id.* at 65:43-44), these general conclusions about individual ingredients do not clearly indicate to a POSA which of the millions of possible claimed combinations of ingredients and concentrations will have the claimed stability.[15] Ex. 1002 ¶ 158. To pass the common structural features test, the specification must do more than just identify ingredients that would be good stabilizers to experiment with—it must show that the particular claimed combinations of ingredients actually correlate with the claimed stability. *See Nuvo*, 923 F.3d at 1380-81; *Pernix*, 323 F. Supp. 3d at 627-29. Without such a correlation, the genus has not been defined with the required precision: a POSA cannot visualize

[15] Indeed, it is telling that the inventors' list of 17 "particularly preferred adalimumab formulations according to the present invention," which they assembled from the PLS modeling, did not include a single formulation with sugar as the claims require, and include eight formulations with mannitol or NaCl, which the claims exclude. Ex. 1001 at 66:65-67:22 (Table M).

or recognize from the specification which species are members of the genus. *See Amgen*, 872 F.3d at 1373. Adding to the confusion is the explicit statement that acetate buffer is a strong destabilizer, which teaches away from at least claims 9-12. Ex. 1002 ¶ 178. Thus, the '039 patent specification fails the common structural features test.

3. *The Additional Stability Data in the '039 Patent Specification Do Not Describe Possession of the Claimed Stability Range*

Although the '039 patent specification contains more empirical stability test data than the provisional patent applications, the data, when viewed by a POSA as a whole, do not establish that any embodiment of the claims falls within the claimed stability range.

a) *The SEC Results Do Not Prove Formulation D-12 Has the Claimed Long-Term Stability*

Table D-2 discloses SEC data for Formulation D-12. Ex. 1001 at 31-33 (Table D-2). As explained, the assay measures protein "monomer" content in a sample of the formulation at time zero, a sample stored for one week at 40° C, and a sample stored for two weeks at 25° C (room temperature). *Id.* SEC, when performed properly, can measure how much of the antibody in a sample is no longer a "monomer," *i.e.* how much has fragmented or formed aggregates over time. Ex. 1002 ¶ 164. The assay does not measure biological activity and cannot determine whether un-aggregated, intact antibody has lost its biological activity due to

chemical degradation, e.g., of amino acid residues that participate in antibody binding. *Id.* Thus, the assay does not show what the claims require: the percentage of biological activity lost. *Id.*

In addition, Table D-2 reports a less-than-one-percent decrease in monomer content after the one- and two-week storage periods: 99.32% monomer at t0 versus 98.53% at t1 (one week at 40° C) and 98.96% at t2 (two weeks at 25° C). Ex. 1001 at 31-33 (Table D-2). The table also reports only a single determination for each t0, t1 and t2 sample. *Id.*; Ex. 1002 ¶ 165. Without performing multiple determinations for each sample and statistical analyses of experimental error, SEC is often not precise enough to reliably quantify such small changes. *Id.* ¶ 166. Without these additional data, a POSA would not have known whether the very small differences in SEC values reported in the specification are statistically significant. *Id.*

In fact, some of the variability in the SEC data reported in the '581 provisional patent application would have caused a POSA to question whether the SEC data for Formulation D-12 in Table D-2 are meaningful. Ex. 1002 ¶ 167. For example, the results in Table 3B indicate that the level of monomer in Formulations 60, 62, 65 and 66 *actually went up* after being stored at 40° C for one week (t1 result higher than t0). *Id* Since there cannot be more monomeric antibody at the end of the stability test than the beginning, a POSA would conclude from these data that the SEC assay has substantial experimental error. *Id.*

b) The RP-HPLC Results Do Not Prove Formulation D-12 Has The Claimed Long-Term Stability

The specification also contains the results of a reverse-phase HPLC ("RP-HPLC") assay on Formulation D-12. *See* Ex. 1001 at 33 (Table D-3). While this assay can quantify some of the chemical degradants that can form during storage, it cannot measure all of them. Ex. 1002 ¶ 170. It also does not measure biological activity. *Id.* Moreover, like for the SEC data, no analysis as to whether these alleged differences were statistically significant is provided. *Id.* A POSA would not have been able to determine from the RP-HPLC data, alone or in combination with the other data reported in the specification, what the biological activity of Formulation D-12 was after one- or two-week storage, never mind after two years. *Id.*

Indeed, the inventors admitted that their RP-HPLC assay did not indicate the stability of Formulation D-12. Ex. 1002 ¶ 171. In the '581 application, which reported the same SEC and RP-HPLC assay for Formulation D-12 (labeled Formulation 42 in the '581 application), the inventors explained that "[a]fter mathematical analysis, the current RP HPLC did not appear to be stability indicating." Ex. 1008 at 27:22-23.

c) The cIEF and CE-SDS Results Do Not Prove Formulation D-12 Has the Claimed Long-Term Stability

The '039 specification also disclosed cIEF and CE-SDS data for Formulation D-12 (and other formulations). Ex. 1001 at 20:10-36. cIEF is a technique that

separates components of a protein mixture into different bands, depending on their overall charge. Ex. 1002 ¶ 172. It can indicate whether charged degradation products have formed over time during storage. *Id.* CE-SDS is similar to cIEF, but separates the proteins into different bands based on overall size. *Id*. Like SEC, it can show whether a protein has fragmented during storage. *Id.* Neither assay, however, measures biological activity. *Id.* And as with the SEC and RP-HPLC data, only single determinations were reported, with no analysis from which statistical significance could be gleaned. *Id.* Moreover, as with their RP-HPLC assay, the inventors reported that these two methods were not good indicators of stability because of the very small changes observed after storage at one and two weeks. According to the inventors, "variance in the [cIEF] data indicates that this method, while useful for characterization, does not appear to be stability-indicating." Ex. 1001 at 30:24-26. Similarly, "variability in the [CE-SDS] method makes it difficult to determine" if the 2-4% changes observed after storage "are real changes." *Id.* at 38:25-29; Ex. 1002 ¶ 172.

4. ***The Specification of the '039 Patent Also Does Not Satisfy §112(a) Written Description Requirement For Claims 2-12***

The specification does not support claims 2-12 any better than claim 1.

Claims 2-4 are genus claims that are almost as broad as claim 1. While claim 2 limits the amount of adalimumab to 40 mg per single dose[16], it does not limit the *concentration* of the adalimumab, which a POSA would understand to be one of the most important variables when making a stable formulation. Ex. 1002 ¶ 174. Similarly, while claim 2 limits the osmolality of the composition to "about 180 to 420 mOsM," a POSA would have understood this range to encompass essentially any practical osmolality for a pharmaceutical composition, and to not meaningfully limit the individual concentrations of adalimumab or other claimed ingredients that could be present in the formulation. *Id.* ¶ 176. And while claim 3 limits the formulation to a pH of "about 5.2," this still spans a range of pH 4.2 to 6.2 (±20%). *See* Ex. 1001 at 7:25-27; Ex. 1002 ¶ 175. The differences between claim 1 and claims 2-4 are immaterial to the "representative species" and "common structural features" tests.

Claims 5-12 require the use of sucrose as the sugar, but like in the provisional applications, the '039 patent specification contains no test data whatsoever to indicate that any sucrose-containing formulation would meet the required stability.

[16] While the term "single dose" has not been defined, reading the description as a whole, the dose can be read to include volumes that result in both high and lower concentration formulations.

Ex. 1002 ¶ 177. It also contains no guidance as to how much sucrose to use, or which of the claimed ingredients to combine it with, to achieve the claimed stability. *Id.* Indeed, none of the tables summarizing the inventors' conclusions as to which ingredients are stabilizing and which are not even mentions sucrose. *See* Ex. 1001, Tables J-L. Also, sucrose is notably absent from Table M, which identifies the inventors' "particularly preferred adalimumab formulations" "[b]ased on the findings in the formulation studies of Blocks A through H." *Id.* at 66:65-67:22 (Table M).

Claims 9-12 require the use of an acetate buffer, but like the provisional applications, there is no disclosure of an embodiment that contains acetate buffer and all of the other limitations of the claims. Ex. 1002 ¶ 178. Moreover, the inventors concluded from their PLS modeling of short-term stability studies that acetate was a "strong destabilizer." Ex. 1001 at 65:43-44. And again, when the inventors put together the Table M list of "particularly preferred" formulations, they omitted acetate. *Id.* at 66:65-67:22 (Table M).

In short, the '039 patent specification fails to provide any better description of claims 2-12 than the provisional patent applications. For the reasons explained above and regarding the provisional applications, the '039 patent specification does not demonstrate to a POSA with reasonable clarity that the inventors possessed the full scope of claims 2-12.

B. Ground 2: The Specification Does Not Enable the Full Scope of Claims 1-12 Given The Extreme Breadth of the Claims, Unpredictability In The Art and Limited Guidance Provided

As explained, section 112(a) separately requires that the specification enable a person of ordinary skill in the art how to make and use the *full scope* of the claims without undue experimentation. *See MorphoSys AG. v. Janssen Biotech, Inc.,* 358 F. Supp. 3d 354, 368-69 (D. Del. 2019) ("[T]he full scope of a claim is not enabled where there is an embodiment within the claim's scope that a person of ordinary skill, reading the specification, would be unable to practice without undue experimentation."). The *Wands* factors confirm that, as with the provisional applications, the '039 patent specification does not enable a POSA to practice the full scope of claims 1-12 without undue experimentation.

1. *The Claims Are Very Broad and Include Difficult-to-Stabilize Embodiments*

The scope of claims 1-12, as discussed, is very broad. *See* Section V.E.1. They encompass millions of different formulations and those formulations will vary significantly in terms of stability.

2. *Extensive Experimentation Is Required To Verify Stability; Indeed, the Alleged Act Of Invention Was Empirical Testing*

The Patent Owner has conceded that "extensive" empirical stability testing is required in order to determine whether a composition containing a particular combination of ingredients at particular concentrations is stable. Ex. 1005 at 216. This is especially true where, as here, the question is whether a particular

composition meets a particular stability limit, such as the upper limit of the claimed stability range. A POSA would need to test compositions covered by the claims to determine whether they met a particular claimed stability level. Ex. 1002 ¶¶ 186-87. If they did not, the POSA would then need to make adjustments to the compositions and re-test as many times as necessary before achieving the required level. If a difficult-to-stabilize formulation proved unworkable, the POSA would need to start over.

Indeed, the specification is explicit that the "nature of the invention" was empirical testing: this is the method used by the inventors to "discover" the claimed subject matter, and the inventors describe a series of empirical testing steps as a "method aspect" of their purported invention "for enhancing long term stability in an aqueous, buffered adalimumab formulation." Ex. 1001 at 4:22-47.

The need for experimentation is aggravated by the fact that the specification does not disclose any type of stability test that correlates with the claimed range of stability tested with methods that measure chemical degradation. Ex. 1002 ¶ 161. A POSA would have no way to evaluate if a formulation had the claimed range of stability, i.e. the claimed range of activity, with the tests measuring chemical degradation disclosed in the application.

3. *The Specification Provides Little Guidance As To Which Compositions Would Meet the Claimed Stability Limits And No Working Examples*

The only example of a formulation that possibly contains the ingredients of claims 1-4 is Formulation D-12, and the specification does not demonstrate that that is a "working" example, i.e., has the claimed stability. Ex. 1002 ¶¶ 159-63. The specification does not provide any examples of ingredient combinations set forth in claims 5-12, working or otherwise. *Id.* ¶ 177. And even if Formulation D-12 was sufficiently stable, a POSA would not know whether the 10 mM of phosphate buffer, polysorbate 80 at 0.1% (w/v), and 240 mM trehalose at pH 5.44-5.32 (Ex. 1001 at 31 (Table D1)) used in formulation D-12 to stabilize adalimumab at a 50 mg/mL concentration would similarly stabilize adalimumab at, for example, 200 mg/ml, in the presence of a different amount of polysorbate 80 and a different type and concentration of sugar, and at a different pH within the claimed range.

Indeed, there are few yardsticks given in the specification that a POSA could use to gauge whether *untested* formulations that span the breadth of claim 1 in fact meet the claimed stability range. For example, while a number of buffers were tested in the specification, the inventors noted that buffer capacity alone cannot be used to predict stability. Ex. 1001 at 60:12-28. Further, as evidenced by the inventors' own results with citrate and phosphate, combining buffers can produce unpredictable results. The unpredictable and unexplained "direct" stabilization of antibody by

phosphate at pH 5.2—a pH where it has virtually no buffering capacity—is one example noted by the inventors. Ex. 1001 at 60:12-28.

At best, the specification offers data that suggests certain buffers, sugars and concentrations to try in, or exclude from, a formulation where other ingredients as tested are kept constant. It also suggests opposite of that which was claimed, for example, that "acetate is a strong destabilizer." Ex. 1001 at 65:43-44; Ex. 1002 ¶ 144. And some claimed ingredients, like sucrose, were not even tested to assess whether they helped or hurt stability. Ex. 1002 ¶ 177. At best, the suggestions in the specification amount to an invitation to experiment. The specification does not disclose any correlation between how the common structural features, namely the combination of ingredients as claimed contributes to the claimed degree of stability, thus it does not avoid the need for serial trial-and-error experimentation.

Moreover, to enable the full scope of the claims, the specification must enable a POSA to make sufficiently stable formulations containing hard-to-stabilize features, such as a high concentration of adalimumab, a pH at or near 4, a sugar like glucose that is a potent oxidizer, and buffers that the specification describes as being strong destabilizers, such as acetate. The specification must also enable a POSA to make formulations that meet the stringent 5% upper end of the claimed stability range. *See Magsil Corp. v. Hitachi Global Storage Techs.*, 687 F.3d 1377, 1384 (Fed. Cir. 2012) (holding the claims invalid because the specification only enabled

a POSA "to achieve a small subset of the claimed range.") The specification contains little or no guidance as to how to make these difficult formulations. Figuring that out would require laborious empirical experimentation, as the Patent Owner acknowledged during prosecution when arguing that the prior art did not render the claims obvious although it did describe a formulation that fell squarely within the scope of the claims with the exception of using a different antibody because it did not present empirical test data demonstrating stability. Ex. 1005 at 216-17.

4. *In Light Of the Above Factors, Making and Using Compounds Covered by the Claims Would Require Undue Experimentation*

Given that the number of compositions covered by the claims is in the millions, they include difficult-to-stabilize compositions such as those with high concentrations of adalimumab, and the specification does not contain any correlation between including particular ingredients or concentrations and achieving the claimed level of stability, extensive and laborious trial-and-error experimentation would be required to practice the full scope of the claims. Essentially, a POSA would have to make and screen each candidate composition for stability, using a test of their own devising, to see whether it was stable for at least 3 months. This is no less than the level of experimentation that the inventors engaged in and later claimed entitled them to a patent. Requiring the public to do the same kind of allegedly

inventive empirical testing as the patentee is the epitome of undue experimentation. *MorphoSys*, 358 F. Supp. 3d at 372 (experimentation undue where a POSA would be required "to do essentially the same amount of work as the inventors of the patents-in-suit").

Thus, for the reasons explained above and regarding the provisional applications, the '039 patents specification does not enable a POSA to practice the full scope of claims 1-12 without undue experimentation.

C. Ground 3: Claims 1-12 Are Indefinite

From the text of the claims alone, the exclusion in claims 1-12 requiring that the composition be "free of . . . citrate and phosphate buffers" is subject to two reasonable constructions: the first is that the claims exclude citrate buffer, phosphate buffer, and the combination of the two. Ex. 1002 ¶ 57. The second is that the claims exclude only the combination. *Id.* Because "buffers" is plural, however, the language of the claim suggests that what is being excluded is not (or not only) a "buffer" made of citrate mixed with phosphate, but any of the three kinds of "buffers." *Id.* ¶¶ 57-59. Moreover, the claim language in the "Further Representative Embodiments" section of the specification make clear that when the applicant wanted to frame claims to exclude just the combination, it used language that made this limitation clear, such as "wherein said ***buffer*** does not comprise ***both of citrate and phosphate***," (Ex. 1001 at 74:16-17, 80:4-5 (emphasis added)), and "wherein

the buffer does not comprise a combination of citrate and phosphate," (*id.* at 77:56-58, 83:43-45), and "the composition is free or substantially free of any citrate/phosphate buffer combination" (*id.* at 86:6-8).

The intrinsic evidence does not sufficiently resolve the ambiguity. The phrase "citrate and phosphate buffers" was not discussed during prosecution of the application. And although the specification states that "the 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," (Ex. 1001 at 66:34-38), the specification is replete with disclosures suggesting that citrate and phosphate buffers alone can be as destabilizing—if not more destabilizing—than a combination of the two. For example:

- Figure 1 reports that phosphate buffer alone was as destabilizing as a buffer that combined citrate and phosphate, and that citrate buffer alone was more destabilizing than the combination. Ex. 1001 at Fig. 1.
- Figure 3 reported that "phosphate and citrate by themselves were weak destabilizers (not to statistical significance). *Id.* at 60:14-16.
- PLS modeling indicated that "both phosphate and citrate are destabilizing, with the effect of phosphate being statistically significant." *Id.* at 65:41-43.

- PLS modeling "indicates that the phosphate and citrate are equally destabilizing." *Id.* at 63:11-16.
- "[C]itrate [w]as the poorest of buffers . . . preferably avoid it." *Id.* at 15:21-23.
- "[T]he destabilizing effect of phosphate is about three-fold greater than for citrate." *Id.* at 64:31-33.
- "[S]ignificant destabilizers" included "NaCl, citrate and phosphate." *Id.* at 62:60-62.

These somewhat contradictory disclosures, when taken as a whole, would have indicated to a POSA that while it was an important aspect of the invention to exclude the combination of citrate and phosphate, the inventors also regarded citrate and phosphate buffers as poor stabilizers and ingredients to avoid in favor of better buffers such as histidine. Ex. 1002 ¶¶ 57-59.

A patent claim is indefinite, and therefore invalid, if, read in light of the specification and prosecution history if fails to inform a POSA with reasonable certainty about the scope of the invention. *Nautilus, Inc. v. Biosig Instruments, Inc*., 134 S. Ct. 2120, 2124 (2014); see also 35 U.S.C. § 112(b); *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1371 (Fed. Cir. 2014) ("The claims, when read in light of the specification and the prosecution history must provide objective boundaries for those of skill in the art."). Here, a POSA would have been confronted with two

reasonable interpretations of the term "citrate and phosphate buffers." Ex. 1002 ¶ 57. Since the claims have more than one reasonable interpretation, holding them to be indefinite under 35 U.S.C. § 112(b) is appropriate. *See* MPEP § 2173.02.

D. CONCLUSION

For the reasons set forth above, claims 1-12 are invalid under 35 U.SC. §§ 112(a) and (b). Petitioner respectfully requests that trial be instituted and that the challenged claims be cancelled.

Dated: September 17, 2019

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: PETITION FOR POST-GRANT REVIEW OF U.S. PATENT NO. 10,155,039 B2 and the exhibits cited therein by *U.S.P.S. Priority Mail Express* on this day, September 17, 2019 on the Patent Owner's correspondence address of record for the subject patent as follows:

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the attached Petition for Post-Grant Review of U.S. Patent No. 10,155,039 contains 14,301 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

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