Filed: June 11, 2017

Filed on behalf of : AbbVie Biotechnology Ltd.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Coherus Biosciences Inc.,
Petitioner,

v.

AbbVie Biotechnology Ltd.,
Patent Owner.

Case IPR2017-01008
U.S. Patent No. 9,085,619

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

I. Introduction....1
II. Background....7
A. The Prior Art....7
1. Gokarn '011 and Gokarn Provisional....7
2. The HUMIRA Label....9
3. Fransson....10
B. The State Of The Art....11
C. The '619 Patent....13
III. Level Of Ordinary Skill In The Art....15
IV. Claim Construction....15
V. Petitioner Fails To Establish That Gokarn '011 Is Entitled To The Earlier Filing Date Of Gokarn Provisional....15
A. Petitioner Fails To Establish Written Description Support For The Subject Matter Relied Upon In The Obviousness Grounds....16
1. Gokarn Provisional does not provide written description support for all IgG antibodies having similar buffering capacity....17
2. Gokarn Provisional does not provide written description support for eliminating buffers for all IgG antibodies at a concentration of 50 mg/ml....20
B. Petitioner Fails To Establish That Gokarn Provisional Supports Claims 162 Or 165 Of Gokarn '011....23
1. Petitioner fails to propose a claim construction for claims 162 or 165....23
2. Claim 162 lacks written description support....24
3. Claim 165 lacks written description support....27
C. The Petition Relies Solely On Priority To Gokarn Provisional....27
VI. The Challenged Claims Would Not Have Been Obvious Over The HUMIRA Label In View Of Fransson And Gokarn '011....28

A. Petitioner Fails To Establish Any Motivation To Remove HUMIRA's Buffering System 29

1. Petitioner does not establish that injection site pain would have motivated one of ordinary skill in the art to eliminate the buffering system from HUMIRA....29

a. Petitioner ignores the multitude of other factors that contribute to injection site pain. 31

b. Fransson does not suggest removing a buffering system 33

c. Other buffering systems were not known to be associated with injection site pain 36

d. "Buffer-free" formulations cited by Petitioner cause injection site pain....37

2. Petitioner fails to show that regulatory or processing cost concerns would have motivated one skilled in the art to remove HUMIRA's buffering system 38

3. Petitioner previously argued that one of ordinary skill would have included a buffer with adalimumab....40

B. Petitioner Fails To Demonstrate A Reasonable Expectation Of Successfully Formulating Adalimumab Without A Buffering System 42

1. Gokarn Provisional's EMAB examples provide no reasonable expectation of successfully preparing the claimed adalimumab formulations....42

2. A formulation designed for one antibody would not have been expected to apply to a different antibody 45

3. Petitioner fails to establish that all IgG antibodies have "highly similar" buffering capacities....51

4. Petitioner fails to address the potential consequences of removing HUMIRA's buffering system....53

5. The cited references do not disclose adalimumab's buffer capacity 55

VII. Ground 2: The Challenged Claims Are Not Obvious Over Gokarn '011 In View Of The HUMIRA Label 58

A. Petitioner Fails To Show That One Of Ordinary Skill In The Art Would Have Been Motivated To Remove HUMIRA's Buffering System....60

B. Petitioner Fails To Demonstrate That A Person Of Ordinary Skill In The Art Would Have Had A Reasonable Expectation Of Success In Arriving At The Claimed Adalimumab Formulations....66

VIII. Conclusion....67

CASES **PAGE**

AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.
759 F.3d 1285 (Fed. Cir. 2014) 25

Alza Corp v. Mylan Labs., Inc.,
464 F.3d 1286 (Fed. Cir. 2006) 44

Amgen, Inc. v. AbbVie Biotechnology Ltd.,
No. IPR2015-01514, Paper 9 (P.T.A.B. Jan. 14, 2016) 50

Amgen, Inc. v. AbbVie Biotechnology Ltd.,
No. IPR2015-01517, Paper 9 (P.T.A.B. Jan. 14, 2016) 51

Ariad Pharm., Inc. v. Eli Lilly & Co.,
598 F.3d 1336 (Fed. Cir. 2010) (en banc) 19, 25

Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.,
776 F.2d 281 (Fed. Cir. 1985) 40

BioDelivery Scis. Int'l, Inc. v. MonoSol Rx, LLC,
No. IPR2015-00167, Paper 6 (P.T.A.B. May 20, 2015) 33

Boston Sci. Corp. v. Johnson & Johnson,
647 F.3d 1353 (Fed. Cir. 2011) 18, 19, 21, 22, 27

Coherus Biosciences, Inc. v. AbbVie Biotechnology Ltd.,
No. IPR2016-01018, Paper 1 (P.T.A.B. May 9, 2016) 40, 41

Coherus Biosciences, Inc. v. AbbVie Biotechnology Ltd.,
No. IPR2016-01018, Paper 10 (P.T.A.B. Nov. 7, 2016).....48

Coherus Biosciences, Inc. v. AbbVie Biotechnology Ltd.,
No. IPR2016-01018, Paper 12 (P.T.A.B. Feb. 2, 2017).....48, 49, 50

Dynamic Drinkware, LLC, v. Nat'l Graphics, Inc.,
800 F.3d 1375 (Fed. Cir. 2015) 23, 27

Ex parte Mann,
No. 2015-003571, 2016 WL 7487271 (P.T.A.B. Dec. 21, 2016) 16, 17

Forty Seven, Inc. v. Stichting Sanquin Bloedvoorziening,
No. IPR2016-01529, Paper 13 (P.T.A.B. Feb. 9, 2017).....22, 25, 27

Genise v. Desautels,
No. 104,834, 2003 WL 21979123 (B.P.A.I. Apr. 17, 2003).....17

Goeddel v. Sugano,
617 F.3d 1350 (Fed. Cir. 2010) 17

In re Magnum Oil Tools Int'l, Ltd.,
829 F.3d 1364 (Fed. Cir. 2016) 28

In re Ruschig,
379 F.2d 990 (C.C.P.A. June 22, 1967).....18

InTouch Techs., Inc. v. VGo Commc'ns, Inc.,
751 F.3d 1327 (Fed. Cir. 2014) 62, 65

Johns Manville Corp. v. Knauf Insulation, Inc.,
No. IPR2015-01633, Paper 10 (P.T.A.B. Jan. 4, 2016) 26

Leo Pharm. Prods., Ltd. v. Rea,
726 F.3d 1346 (Fed. Cir. 2013) 34, 40, 63, 65

Nichia Corp. v. Everlight Ams., Inc.,
Nos. 2016-1585/-1618, 2017 WL 1521595 (Fed. Cir. Apr. 28, 2017) 54

Noelle v. Lederman,
355 F.3d 1343 (Fed. Cir. 2004) 19

Novartis Pharm. Corp. v. Watson Labs., Inc.,
611 F. App'x 988 (Fed. Cir. 2015) 61

Novozymes A/S v. DuPont Nutrition Biosciences APS,
723 F.3d 1336 (Fed. Cir. 2013) 21

Redline Detection, LLC v. Star Envirotech, Inc.,
811 F.3d 435 (Fed. Cir. 2015) 34

Regents of Univ. of Cal. v. Eli Lilly & Co.
119 F.3d 1559 (Fed. Cir. 1997) 25

Star Sci., Inc. v. R.J. Reynolds Tobacco Co.,
655 F.3d 1364 (Fed. Cir. 2011) 44

TRW Auto. US LLC v. Magna Elecs., Inc.,
No. IPR2014-00258, Paper 18 (P.T.A.B. Aug. 27, 2014).....30

Unigene Labs., Inc. v. Apotex, Inc.,
655 F.3d 1352 (Fed. Cir. 2011) 32, 33

X2Y Attenuators, LLC v. ITC,
757 F.3d 1358 (Fed. Cir. 2014) 24

Zimmer Biomet Holdings, Inc. v. Four Mile Bay, LLC,
No. IPR2016-00011, Paper 8 (P.T.A.B. Apr. 1, 2016) 26

STATUTES

35 U.S.C. § 102 ..... 15, 16

35 U.S.C. § 112 .....3, 17

35 U.S.C. § 312 28

35 U.S.C. § 371 27

OTHER AUTHORITIES

37 C.F.R. § 42.22 28

37 C.F.R. § 42.65 .....26, 30, 47, 55, 57

PATENT OWNER EXHIBIT LIST

EXHIBIT	DESCRIPTION
2001	Wang, "Instability, Stabilization, and Formulation of Liquid Protein Pharmaceuticals*," Int'l J. Pharmaceutics 185*, 129-188 (1999)
2002	Jorgensen, et al., "Pain Assessment of Subcutaneous Injections," *Ann. Pharmacotherapy 30*, 729-732 (July/Aug. 1996)
2003	Brazeau, et al., "Current Perspectives on Pain upon Injection of Drugs," *J. Pharm. Sci. 87*(6), 667-677 (June 1998)
2004	Declaration of Mark C. Manning, Ph.D. dated May 6, 2016 from IPR2016-01018, Ex. 1002.
2005	Kuzu, et al., "The Effect of Cold on the Occurrence of Bruising, Haematoma and Pain at the Injection Site in Subcutaneous Low Molecular Weight Heparin" *Int'l J. Nursing Studies 38*, 51-59 (2001)
2006	Jorgensen, "Improvement of Patient Convenience in Treatment with Growth Hormone," *J. Pediatric Endocrinology 7*(2), 175-180 (1994)
2007	*Not Used*
2008	Ipp, et al., "Adverse Reactions to Diphtheria, Tetanus, Pertussis-Polio Vaccination at 18 Months of Age: Effect of Injection Site and Needle Length," *Pediatrics 83(*5): 679-682 (May 1989)
2009	Liu, et al., "Reversible Self-Association Increases the Viscosity of a Concentrated Monoclonal Antibody In Aqueous Solution," *J. Pharm. Sci. 94*(9), 1928-1940 (Sept. 2005).
2010	*Not Used*

EXHIBIT	DESCRIPTION
2011	Veys, et al., "Pain at the Injection Site of Subcutaneously Administered Erythropoietin: Phosphate-Buffered Epoetin Alpha Compared to Citrate-Buffered Epoetin Alpha and Epoetin Beta," *Clin. Nephrology 49*(1), 41-44 (1998)
2012	Yu, et al., "Pain Perception Following Subcutaneous Injections of Citrate-Buffered and Phosphate-Buffered Epoetin Alpha," *Int'l J. Artificial Organs 21*(6), 341-343 (1998)
2013	Carpenter & Manning, eds., *Rational Design of Stable Protein Formulations, Theory and Practice*, *Pharmaceutical Biotechnology 13* (Kluwer Academic/Plenum Publishers, New York) (2002)
2014-2015	*Not Used*
2016	Chi, et al., "Physical Stability of Proteins in Aqueous Solution: Mechanism and Driving Forces in Nonnative Protein Aggregation," *Pharm. Res. 20*(9), 1325-1336 (Sept. 2003)
2017-2019	*Not Used*
2020	Lee, et al., "Toward Aggregation-resistant Antibodies by Design," *Trends in Biotech. 31*(11), 612-620 (2013)
2021	Daugherty, et al., "Formulation and Delivery Issues for Monoclonal Antibody Therapeutics," *Adv. Drug Deliv. Rev. 58,* 686-706 (2006)
2022-2024	*Not Used*
2025	Kamerzell, et al., "Increasing IgG Concentration Modulates the Conformational Heterogeneity and Bonding Network that Influence Solution Properties," *J. Phys. Chem. B. 113*(17), 6109-6118 (2009)

EXHIBIT	DESCRIPTION
2026	Salinas, et al., "Understanding and Modulating Opalescence and Viscosity in a Monoclonal Antibody Formulation," *J. Pharm. Sci. 99*(1), 82-93 (2010)
2027	Helms, et al., "Destabilizing Loop Swaps in the CDRs of an Immunoglobulin V_L Domain," *Protein Sci. 4*, 2073-2081 (1995)
2028	Rouet, et al., "Stability Engineering of the Human Antibody Repertoire," *FEBS Letters 588*, 269-277 (2014)
2029-2032	*Not Used*
2033	Fayos, et al., "On the Origin of the Thermostabilization of Proteins Induced by Sodium Phosphate," *J. Am. Chem. Soc. 127*(27), 9690–9691 (2005)
2034	Mezzasalma, et al., "Enhancing Recombinant Protein Quality and Yield by Protein Stability Profiling," *J. Biomolecular Screening 12*(3), 418-428 (2007)
2035	Ruiz, et al., "Aggregation of Recombinant Human Interferon Alpha 2b in Solution: Technical Note," *AAPS Pharm. Sci. Tech. 7*(4), Article 99, E1-E5 (2006)
2036	Chen, et al., "Aggregation Pathway of Recombinant Human Keratinocyte Growth Factor and Its Stabilization," *Pharm. Res. 11*(11), 1581-1587 (1994)
2037	*Not Used*
2038	Raibekas, et al., "Anion Binding and Controlled Aggregation of Human Interleukin-1 Receptor Antagonist," *Biochemistry 4*(29), 9871-9879 (2005)
2039	Carpenter, et al., "Rational Design of Stable Lyophilized Protein Formulations: Some Practical Advice," *Pharm. Res. 14*(8), 969-975 (1997)
2040	*Not Used*

EXHIBIT	DESCRIPTION
2041	Gokarn, et al., "Self-Buffering Antibody Formulations," *J. Pharm. Sci. 97*(8), 3051-3066 (Aug. 2008)
2042	Humphreys, "Top 200 Medicines - Special Report," Pharmalive (Aug. 12, 2015), http://www.pharmalive.com/special-report-top-200-medicines/
2043	Coherus, U.S. Serial No. 14/879,847, Response to Non-Final Office Action dated April 21, 2017
2044	Coherus, U.S. Serial No. 14/879,885, Pre-Appeal Brief Request for Review dated January 17, 2017
2045	Coherus, U.S. Serial No. 14/643,844, Amendment dated August 24, 2015
2046-2048	*Not Used*
2049	Barnett, et al., "Reduction of Pain and Local Complications When Buffered Lidocaine Solution Is Used as a Local Anesthetic in Conjunction with Hyperthermia Treatments: Results of a Randomized Trial," *Int'l J. Radiation Oncology Biol. Phys. 23*(3), 585-591 (1992)
2050	*Not Used*
2051	Shire, "Formulation of Proteins and Monoclonal Antibodies (mAbs)," *Monoclonal Antibodies, Meeting the Challenges In Manufacturing, Formulation, Delivery and Stability of Final Drug Product, Woodhead Publishing Series in Biomedicine 77,* Chap. 4, 93-120 (Woodland Publishing, Cambridge, UK) (2015)
2052-2054	*Not Used*
2055	ZEVALIN® Label, Physicians' Desk Reference (Thomson PDR, Montvale, N.J., 60th ed.) (2006)

I. Introduction

In four separate Petitions, Coherus Biosciences Inc. ("Petitioner") challenges claims 16-19 and 24-30 of AbbVie Biotechnology Ltd.'s ("AbbVie") U.S. Patent No. 9,085,619 ("the '619 patent") directed to high concentration (50-200 mg/ml) aqueous pharmaceutical formulations comprising adalimumab (the active ingredient in HUMIRA®) without a buffering system. (IPR2017-00822, IPR2017-00823, IPR2017-01008, IPR2017-01009.) Each of the Petitions is flawed and should be denied for the reasons set forth in Patent Owner's respective preliminary responses.

Here, Petitioner presents two proposed grounds of unpatentability: (1) obviousness over the *Physicians' Desk Reference* (58th ed. 2004) entry for HUMIRA ("HUMIRA Label") (Ex. 1205) in view of Fransson (Ex. 1219) and U.S. Patent Pub. No. 2016/0319011 ("Gokarn '011") (Ex. 1203); and (2) obviousness over Gokarn '011 in view of the HUMIRA Label. Petitioner asserts Gokarn '011 is prior art as of the June 14, 2005 filing date of U.S. Serial No. 60/690,582 ("Gokarn Provisional") (Ex. 1204; Pet., 1.) Each asserted ground relies on Gokarn Provisional's disclosure rather than any material added in a later-filed application. (Pet., 1, 8.) The Board should deny the Petition in its entirety because both grounds are factually unsupported and legally deficient.

At the outset, Petitioner does not establish that Gokarn '011 is entitled to the June 14, 2005 filing date of Gokarn Provisional. To obtain that effective date, Petitioner must show that Gokarn Provisional provides written description support for both (1) the subject matter relied on in Gokarn '011 to allege obviousness, and (2) at least one claim of Gokarn '011. (Pet., 24.) Petitioner does neither.[1]

Gokarn Provisional lacks written description support for the subject matter on which Petitioner attempts to rely for its obviousness challenges. Gokarn Provisional does not disclose adalimumab, *any* monoclonal antibody solution without a buffering system, or *any* monoclonal antibody solution at a concentration of 50-200 mg/ml in *any* formulation, let alone in a formulation without a buffering system. Despite this, Petitioner nevertheless alleges that Gokarn Provisional discloses that IgG antibodies at high concentrations can control pH without buffers. But Petitioner's central assertion is unsupported because Gokarn Provisional *does*

[1] Importantly, Petitioner does not assert that Gokarn '011 is entitled to any other filing date within its chain of priority applications. The Petition, for example, does not rely on any material contained in any later application to allege obviousness. Consequently, Gokarn '011 is only entitled to its July 19, 2016 filing date, which is not prior art to the '619 patent.

not disclose the IgG class of antibodies. Nor does the generic recitation of "proteins" and "antibodies" and a single disclosed protein called "AMG412 (EMAB)" (also referred to as "EMAB") support the entire class of IgG antibodies.

Gokarn Provisional also fails to disclose the claimed concentration of 50-200 mg/ml of *any* antibody formulation without a buffering system. Rather, the only examples used a *different antibody from adalimumab* (*i.e.,* EMAB), in a *buffered* solution, at a concentration (46 mg/ml) *below* the claimed concentration (50-200 mg/ml). Indeed, Gokarn Provisional evidences a *failure* to achieve even a 50 mg/ml concentration for the only antibody Gokarn attempted to formulate. Because Gokarn Provisional does not disclose the subject matter Petitioner relies on for obviousness, Gokarn '011 is not prior art.

Gokarn '011 also is not prior art because Petitioner fails to show that Gokarn Provisional provides written description support for any claim of Gokarn '011. Petitioner alleges that Gokarn Provisional discloses "bufferless, high concentration EMAB solutions" that support claims 162 and 165 of Gokarn '011. (Pet., 26-29.) But both EMAB examples in Gokarn Provisional *included buffers*. At most, Gokarn Provisional describes a research plan, which is inadequate for written description support under 35 U.S.C. § 112. For this independent reason, Gokarn '011 is not prior art.

Because both Ground 1 and Ground 2 rely on Gokarn '011 in combination with other references, institution should be denied with respect to both grounds. But even if Gokarn '011 is considered to be prior art (which it is not) by incorporating by reference the disclosure of Gokarn Provisional, Petitioner fails to establish both a motivation to combine and a reasonable expectation of success for each of its two grounds.

With respect to Ground 1, Petitioner fails to establish that one of ordinary skill in the art would have been motivated to combine the HUMIRA Label with Fransson and Gokarn '011 to generate a high concentration (50-200 mg/ml) aqueous adalimumab pharmaceutical formulation without a buffering system. The HUMIRA Label discloses a *buffered* adalimumab formulation. Although the HUMIRA Label mentions injection site pain, there were a multitude of potential contributors to such pain, and an even larger number of potential avenues to address each one. Nothing in the HUMIRA Label or other cited references would have provided any motivation to modify the already highly successful HUMIRA formulation to address such pain by removing HUMIRA's buffering system.

Fransson makes no mention of HUMIRA. It instead reports an investigation into tolerance of subcutaneous injection site pain with *buffered* protein solutions of human insulin-like growth factor 1 (hIGF-1). No reason existed to combine these

buffered solutions of Fransson with either the HUMIRA Label or Gokarn Provisional, both of which concerned different antibodies.

Even if combined, the cited references would not have led to the claimed invention. Critically, Fransson never discloses or suggests removing a buffering system. Rather, Fransson proposes to address injection site pain by using a different buffer, decreasing (but not eliminating) the buffer concentration, or changing the solution's pH. In fact, Fransson reports that no further reduction in injection pain was observed when the buffer concentration of the solution was decreased below a certain threshold. Fransson also points to some of the dozens of other known potential causes of injection site pain, including injection volume, speed of injection, injection site, the size and quality of the injection needle, and other factors. Therefore, Petitioner's hindsight-driven assertion that Fransson would have motivated a skilled artisan to remove HUMIRA's buffering system is refuted by Fransson's disclosure.

In addition, given the lack of meaningful guidance in Gokarn Provisional, one of ordinary skill in the art would have had no reasonable expectation of success in preparing the claimed adalimumab formulations by removing the buffering system from the highly successful HUMIRA formulation. As the Board found in prior IPR decisions, the scientific literature in 2007 was replete with evidence showing that a formulation designed for one antibody could not

reasonably be expected to be successfully applied to a different antibody, such as adalimumab. The positions that Petitioner advocates here regarding buffers and the state of the art also cannot be reconciled with positions it has taken before this Office in prosecuting Petitioner's own patent applications, which also purport to cover formulations of adalimumab. For all these reasons, Petitioner has failed to establish a reasonable likelihood of prevailing on Ground 1, and institution of that ground should be denied.

For similar reasons, Petitioner also fails to establish both a motivation to combine and a reasonable expectation of success with respect to Ground 2. In fact, Petitioner does not identify *any* problem with HUMIRA that would have motivated a skilled artisan to remove the buffering system described in its label. This is a fatal deficiency. Nor does Petitioner establish a reasonable expectation of success in preparing the claimed adalimumab formulations by removing the buffering system from the existing HUMIRA formulation given the minimal disclosure in Gokarn Provisional and the high level of unpredictability and lack of any reasonable expectation of success associated with removing a buffering system from an antibody formulation. Thus, Petitioner does not present a viable obviousness theory.

For these reasons, which are explained in more detail below, Petitioner has not shown that it is likely to prove that any challenged claim is unpatentable. The Board should therefore deny institution of the Petition.

II. Background

A. The Prior Art

1. Gokarn '011 and Gokarn Provisional

Gokarn '011 was filed on July 19, 2016, and claims priority to Gokarn Provisional, filed June 14, 2005. (Ex. 1203.) Gokarn Provisional differs significantly from Gokarn '011, in part, because Gokarn '011 includes different examples and a much lengthier specification. (*Compare* Ex. 1203 *with* Ex. 1204.) In its obviousness allegations, Petitioner relies on Gokarn Provisional, rather than any material added in Gokarn '011. (*See, e.g.*, Pet., 44-51, 57-61 (contending Gokarn Provisional is incorporated by reference into Gokarn '011).)

Gokarn Provisional purports to describe an ongoing investigation into potential protein formulations. (Ex. 1204.)[2] It consists of three-pages of text, a short PowerPoint presentation, and one claim. (*See generally* Ex. 1204; Pet., 26 n.2.) The text alleges very generally that potentially "self-buffering" formulations

[2] All citations herein refer to the exhibits' native page numbers, except IPR numbers are used where the exhibits do not include native page numbers.

may be made using an incredibly broad and undefined class of pharmaceutical proteins, including "large, and small proteins, as well as different antibodies, naturally or non-naturally occurring peptides and proteins, including peptibodies, maxibodies, interbodies, etc." (Ex. 1204, 2:10-15.) Gokarn Provisional also states that an "active protein" may be the "primary source" of buffering, although "[o]ther traditional buffering agents may be present," such as acetate, citrate, and other buffers. (*Id.,* 1:9-25.) Gokarn Provisional states that a protein's potential for providing buffering capacity depends on "the presence of enough . . . charged amino acid residues including glutamic acid, aspartic acid, histidine, arginine, and lysine . . . ." (*Id.*, 2:18-23.) Gokarn Provisional states that this adequate buffer capacity requires the protein to be at "sufficiently high" concentration but reveals no specific concentration range. (*Id.*, 1:5-9.)

Gokarn Provisional does not disclose adalimumab. It identifies only one specific protein, EMAB. (*Id.*, 4-5.) But it does not provide the structure, amino-acid sequence, or any other description of EMAB. (*See id.*)

Gokarn Provisional contains two examples in which buffered solutions of EMAB are prepared. (*Id.*) The first example describes the preparation of *acetate-buffered* EMAB solutions. (*Id.*, 4.) The solutions were concentrated to 46 mg/ml, at which point they became "cloudy." (*Id.*) The second example describes the

preparation of *succinate-buffered* EMAB solutions. (*Id.*, 5.) The solutions were concentrated to 45 mg/ml, at which point cloudiness appeared. (*Id.*)

Over the next several PowerPoint slides, Gokarn Provisional shows an attempt to extrapolate EMAB's buffering capacity by comparing the acetate- and succinate-buffered solution examples to an acetate buffer standard. (*Id.,* 6-13.) It states, however, that "[a] more accurate estimate of the buffer capacity from EMAB alone will have to be obtained from bufferless high concentration EMAB solutions." (*Id.*, 13.) Gokarn Provisional describes those investigations as "on-going." (*Id.*)

2. The HUMIRA Label

The HUMIRA Label (Ex. 1205, 470) concerns AbbVie's HUMIRA pharmaceutical adalimumab product, initially approved in 2002 for treating moderately to severely active rheumatoid arthritis. HUMIRA's prescribing information was cited during prosecution of the '619 patent. (Ex. 1201, 3.) The HUMIRA Label states that adalimumab is a recombinant human IgG1 human monoclonal antibody that binds specifically to TNF-alpha. (Ex. 1205, 470.) It states that adalimumab consists of 1330 amino acids and has a molecular weight of 148 kilodaltons. (*Id*.) It states that 40 mg adalimumab is administered subcutaneously with a single-use, pre-filled syringe containing 0.8 ml of product. (*Id.*, 472.)

The HUMIRA Label describes the composition of AbbVie's marketed HUMIRA product, which is *buffered* with a dual citrate-phosphate buffering system. The HUMIRA Label does not disclose formulations that do not contain a buffering system, nor does it identify any need to reduce or eliminate buffers.

The HUMIRA Label lists adverse events experienced in rheumatoid arthritis clinical trials, including respiratory, gastro-intestinal, laboratory testing, and "other" events, including injection site pain. (*Id*., 472.) The only listed adverse events leading to discontinuation of HUMIRA treatment are "clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%)." (*Id.*) The HUMIRA Label states that most injection site reactions were described as mild and did not necessitate discontinuation. (*Id*.) The HUMIRA Label does not identify any cause of injection site reactions or suggest any connection with the buffering system.

3. Fransson

Fransson is a journal article titled "Local Tolerance of Subcutaneous Injections." (Ex. 1219, 1012.) It reports the results of a ten-subject study on how pH and buffer concentration might affect local tolerance to subcutaneous injection of solutions of hIGF-1, but says nothing about formulation or injection of antibodies, much less HUMIRA. (*Id.*, 1012-13.)

Fransson analyzes eight hIGF-1 solutions having a varying pH (6.0 or 7.0) and varying concentrations of phosphate buffer: 5 mM, 10 mM, 50 mM. (*Id.*, 1013

(Table 2 listing formulations A-H).) Fransson used phosphate buffer as an alternative to citrate, stating that "citrate buffer causes pain." (*Id.*, 1012.) Fransson also points to some of the many other known potential causes of injection pain, including injection volume, speed of injection, injection site, the size and quality of the injection needle, and other factors. (*Id.*)

Compared to the higher 50 mM phosphate-buffered solutions of hIGF-1, Fransson reports that the intermediate 10 mM phosphate-buffered solutions generated less injection pain. (*Id.*, 1014.) Further reduction to 5 mM phosphate, however, "did not reduce pain further." (*Id.*) Fransson does not disclose or suggest eliminating buffer to minimize injection pain. Fransson also reports that increasing pH reduces injection pain, with solutions at a pH of 6.0 causing more pain than those at a pH of 7.0. (*Id.*, 1014-15.)

B. The State Of The Art

The buffered adalimumab formulation of HUMIRA was a breakthrough in the field of antibody therapeutics when it was approved in 2002. (Ex. 2042.) HUMIRA was the first commercialized high-concentration, liquid antibody formulation for subcutaneous administration. (*Id*.) HUMIRA was successfully formulated as a *buffered* pharmaceutical formulation and is one of the top selling drugs in the world. (Ex. 1205, 470; Ex. 2042, 1.) At the time of the invention of the '619 patent, HUMIRA was the only monoclonal antibody formulation

approved for subcutaneous administration that was liquid rather than lyophilized—a testament to its remarkable formulation. (*See, e.g.,* Ex. 1286, 2-4 (Table 1).)

Like HUMIRA, all of the fifteen approved aqueous monoclonal antibody products available between 2003 and 2007 were provided with a buffering system. (Ex. 1286, 2-4; Ex. 2055, 852.) The same held true as late as 2015. (Ex. 2051, 94-101 (Table 4.1); Ex. 2055, 852.)

At the time of the '619 patent invention, those skilled in the art used buffering systems because it was extremely difficult to make stable (*e.g.,* non-aggregated, non-fragmented, non-degraded, non-denatured, etc.), liquid pharmaceutical formulations of antibodies, particularly at high concentrations. (Ex. 1286, 5, 14; *see, e.g.*, Ex. 1201, 2:56-62 ("difficulties with the aggregation, insolubility, and degradation of proteins generally increase as protein concentrations in formulations are raised").) Even after HUMIRA's introduction, the scientific literature reported the use of buffering systems, such as citrate, to produce a successful formulation. (*See* Ex. 2028, 271; Ex. 2020, 612; Ex. 2026, 82.) The initial formulation of ERBITUX, for example, had antibody aggregation problems, which those skilled in the art addressed by empirically optimizing conditions and using citrate buffer. (*See id.*; *see also* Ex. 1201, 3:66-4:2 (stating that traditional formulations use buffering systems).)

The complexity and unpredictability of formulating antibodies resulted, at least in part, because a formulation designed for one antibody would not reasonably have been expected to be successfully applied to a different antibody. (*See, e.g.,* Ex. 2021, 690.) Indeed, it was well established by 2007 that antibodies had to be evaluated *individually* when developing a liquid formulation because of their differing structures and properties. (Ex. 1286, 5, 14, 21.) This was true even for antibodies with similar sequences and among antibodies of the same class (*e.g.,* IgG or IgG1). (*Id*.; Ex. 2021, 690.)

C. The ’619 Patent

The ’619 patent details the surprising discovery that adalimumab formulated in water at high concentrations *without* a buffering system may be used as a pharmaceutical formulation. (*See* Ex. 1201, 3:29-33.) Contrary to the traditional approaches for protein formulation, the ’619 patent describes and claims high concentration (50-200 mg/ml) aqueous pharmaceutical formulations comprising adalimumab without a buffering system. (*See, e.g.*, *id.*, 60:47-62:32 (Table 12) & claims 16-18.)

While conducting experiments for a different but related purpose, the inventors made several observations that led them to use diafiltration techniques to produce adalimumab in pure water at concentrations ranging from 10 mg/ml to above 200 mg/ml. (*See, e.g.*, *id.*, 51:47-54:18, 60:47-62:32.) The ’619 patent

describes the resulting formulations as unexpectedly non-opalescent. (*See, e.g.*, *id.*, 60:6-16, 68:37-49.) That is, surprisingly, the formulations were clear, with no solution haziness or precipitation. (*Id.*, 44:47-57, 60:25-36.) The formulations were also "surprisingly stable," with only minimal protein aggregation even at adalimumab concentrations of 200 mg/ml, and "virtually no instability phenomena" were observed. (*Id.*, 67:30-45, 68:52-55.) The '619 patent also discloses that adalimumab formulations without a buffering system had low viscosity at concentrations up to 200 mg/ml—a key property for a subcutaneously administered formulation. (*Id.*, 3:1-7, 60:17-20.) The patent contrasts the low viscosity of the adalimumab formulation without a buffering system with another protein (human serum albumin) formulation without a buffering system, which exhibited a six-fold *increase* in viscosity compared to a buffered formulation. (*Id.*, 65:1-10 (concluding that viscosity "may depend on the individual protein").)

The '619 patent claims are directed to the disclosed high-concentration adalimumab pharmaceutical formulations lacking a buffering system, which achieved the unexpected properties of low aggregation, low opalescence, low viscosity, and high solubility. (*Id.*, 151:9-152:66.) Independent claim 16 defines an aqueous pharmaceutical formulation comprising an antibody having the complementarity determining region (CDR) amino acid sequences of adalimumab,

an antibody concentration of 50-200 mg/ml, and water, in which the formulation does not comprise a buffering system. (*Id.*, 152:15-32.)

At the time of AbbVie's invention, *no one* had successfully developed a commercial high concentration monoclonal antibody pharmaceutical formulation without a buffering system.

III. Level Of Ordinary Skill In The Art

For the limited purpose of this Preliminary Response, Patent Owner does not contest Petitioner's proposed level of ordinary skill in the art. (Pet., 22.)

IV. Claim Construction

Patent Owner believes construction of the phrase "does not comprise a buffering system" is unnecessary at this stage. For purposes of this Preliminary Response only, Patent Owner does not dispute Petitioner's proposed construction: "contains no more than a *de minimis* amount of extrinsic buffer." (Pet., 22-23.)

V. Petitioner Fails To Establish That Gokarn '011 Is Entitled To The Earlier Filing Date Of Gokarn Provisional

Petitioner contends that Gokarn '011 is prior art to the challenged claims under 35 U.S.C. § 102(e) (pre-AIA) as of Gokarn Provisional's June 14, 2005 filing date. (Pet., 1, 23-34.) But as shown below, Petitioner fails to prove that Gokarn '011 qualifies as prior art.

Only two of Gokarn '011's related applications were filed before the '619 patent's earliest priority date (November 2007): PCT Patent Pub. No.

WO2006/138181 ("Gokarn PCT") (Ex. 1241) and Gokarn Provisional. (Ex. 1203). Here, Petitioner relies *only* on Gokarn Provisional's filing date as the effective date under Section 102(e). (Pet., 33-34.) To rely on this date, Petitioner must show that Gokarn Provisional provides written description support for both: (1) the subject matter relied on in Gokarn '011 to allege obviousness, and (2) at least one claim of Gokarn '011. *Ex parte Mann*, No. 2015-003571, 2016 WL 7487271, at *5-6 (P.T.A.B. Dec. 21, 2016). Petitioner fails to show this required support; thus, Gokarn '011 is not entitled to Gokarn Provisional's filing date.

A. Petitioner Fails To Establish Written Description Support For The Subject Matter Relied Upon In The Obviousness Grounds

Gokarn Provisional *does not disclose adalimumab*, a monoclonal antibody formulation without a buffering system, or a monoclonal antibody at a concentration of 50-200 mg/ml, much less a composition with all these claimed components. Petitioner nevertheless alleges that Gokarn Provisional discloses that IgG antibodies can control pH in a liquid formulation without the need for traditional buffering agents. (Pet., 44, 48, 53.) Petitioner also alleges that Gokarn Provisional discloses that an "IgG1 antibody" does not need traditional buffering agents at a concentration of 30-50 mg/ml in the pH range of 4.5-5.5, and at 50 mg/ml in the pH range of 5.0-5.5. (Pet., 57.)

A threshold question, however, is whether Gokarn '011 is entitled to the date of Gokarn Provisional as to this subject matter. *Mann*, 2016 WL 7487271, at *5 (vacating Section 102(e) rejection because the examiner failed to demonstrate Section 112 support in an earlier provisional application for the subject matter relied on in the rejection). It is not.

Citing only its obviousness analysis, Petitioner never addresses whether Gokarn Provisional provides *written description* support for the subject matter upon which Petitioner relies. (*See* Pet., 33-34.) Gokarn '011 cannot be accorded priority to Gokarn Provisional's filing date because Petitioner failed to meet its burden of proving entitlement to that date under Section 112. *See Genise v. Desautels*, No. 104,834, 2003 WL 21979123, at *17 (B.P.A.I. Apr. 17, 2003) ("written description concerns what the specification shows as *being possessed by these particular inventors*, not what would have been obvious" in light of the specification)[3]; *Goeddel v. Sugano*, 617 F.3d 1350, 1356 (Fed. Cir. 2010).

1. Gokarn Provisional does not provide written description support for all IgG antibodies having similar buffering capacity

Gokarn Provisional contains only three pages of text, ten PowerPoint slides, and one claim. (Ex. 1204.) Gokarn Provisional does not disclose adalimumab.

[3] In this paper, all emphases are added unless otherwise indicated.

Gokarn Provisional does not disclose the class of IgG antibodies or the subclass of IgG1 antibodies. Instead, it only vaguely mentions the extremely broad categories of "pharmaceutical proteins," "antibodies," and "peptibodies, maxibodies, interbodies, etc." (Ex. 1204, 2:10-15.) Gokarn Provisional also refers to a "given class of monoclonal antibodies," but does not identify or define the class of antibodies, let alone identify the class of IgG antibodies or subclass of IgG1 antibodies from among that broader class. (Ex. 1204, 3:7-8.) This generic and vague disclosure related to antibodies and the failure to specifically describe IgG antibodies does not satisfy the written description requirement for IgG (or IgG1) antibodies. *In re Ruschig*, 379 F.2d 990, 993-94 (C.C.P.A. June 22, 1967) (a generic chemical structure did not describe a chemical species); *Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1367 (Fed. Cir. 2011) (a chemical genus did not describe a specific species or sub-genus).

Petitioner asserts that Gokarn Provisional suggests that IgG antibodies have adequate buffering capacity to provide pH control, because it states that "[a]ntibodies at sufficiently high concentrations possess adequate buffering capacity." (Pet., 36-37, 43, 60 (citing Ex. 1204, 1:5-8).) But this statement does not provide the necessary precision required to describe a genus, "such as by structure, formula, or chemical name." *Boston Sci.*, 647 F.3d at 1363 (citation omitted).

In addition to *not* identifying IgG antibodies as a class or IgG1 antibodies as a subclass, Gokarn Provisional's vague mention of "sufficiently high concentrations" does not identify any particular antibody concentration or any particular class of antibody. (Ex. 1204, 1:6); *see Boston Sci.*, 647 F.3d at 1368-69 (holding that a specification's "meager disclosure" of "analogs" failed to disclose a narrower sub-genus of analogs "by name, by functionality, or even by implication"). Gokarn Provisional's use of broad language to express a hypothesis that "bufferless" formulations may be possible for an undefined class of proteins represents, at most, an invitation to conduct further research, which is insufficient as a matter of law for written description. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1357-58 (Fed. Cir. 2010) (en banc).

The only antibody that Gokarn Provisional specifically identifies is EMAB. (Ex. 1204, 4-5.) It does not give EMAB's structure, sequence, or classify it as an IgG, let alone an IgG1 antibody. (Ex. 1204.) This limited disclosure of *only* EMAB cannot provide written description support for an entire class of antibodies encompassing different sequences, structures, and functions. *See Noelle v. Lederman,* 355 F.3d 1343, 1350 (Fed. Cir. 2004).

Gokarn Provisional therefore does not provide written description of the subject matter Petitioner relied on for obviousness—a class of antibodies purportedly capable of "self-buffering." (Pet., 36-37.)

2. Gokarn Provisional does not provide written description support for eliminating buffers for all IgG antibodies at a concentration of 50 mg/ml

Petitioner contends that Gokarn Provisional discloses that a separate buffering agent is unnecessary and can be removed for all IgG antibodies at a concentration of 50 mg/ml. (Pet., 42, 44, 57.) But Gokarn Provisional does not identify a specific concentration at which all IgG antibodies allegedly would not require a buffering system. Nor does it disclose any antibody formulation at any concentration that lacks a buffering system.

Gokarn Provisional does not define any "high concentration" threshold for the entire class of IgG antibodies. Although Petitioner contends that "high concentration" for IgG1 antibodies means "specifically 50 mg/ml in the 5.0-5.5 pH range," Gokarn Provisional contains no such disclosure. (*See* Pet., 57.) Instead, it provides only two examples of the preparation of buffered solutions of EMAB, neither of which reached a protein concentration of 50 mg/ml. (Ex. 1204, 4-5.) The first example concentrated EMAB to a maximum of only 46 mg/ml, at which point the solution became "cloudy." (*Id.*, 4.) The second example prepared a 45 mg/ml EMAB solution, again reaching the maximum concentration at which "cloudiness appear[ed]." (*Id.*, 5.) Neither Petitioner nor its declarants address Gokarn Provisional's inability to formulate EMAB, even in a *buffered* solution, at a

concentration higher than 46 mg/ml. (*See* Pet., 9, 38, 40; *see also* Ex. 1202, ¶¶81-88, 90-92.)

While Gokarn Provisional attempts to *predict* by extrapolation the buffering performance of an EMAB solution at 50 mg/ml (Ex. 1204, 9), it never describes any EMAB solution capable of actually achieving a 50 mg/ml concentration, let alone up to 200 mg/ml. This is a fatal deficiency. *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013) ("[I]f Novozymes had possessed a working [example] . . . it surely would have disclosed that [example] instead of, or at least along with, the nonfunctional [example] . . . ."). Thus, Gokarn Provisional does not provide written description support for an aqueous antibody formulation with a concentration of 50-200 mg/ml. Rather, it describes a *failure* to achieve even 50 mg/ml for the only antibody for which formulation was attempted (EMAB). (*See* Ex. 1204, 4-5.) Gokarn Provisional also does not purport to extend the 50 mg/ml concentration to any other antibody, nor does it use 50 mg/ml to provide any "precise definition" of a broader genus of antibodies encompassing EMAB. (*Id.*); *Boston Sci.*, 647 F.3d at 1363.

Moreover, Gokarn Provisional does not provide written description support for any formulation of any IgG antibody without a buffering system. Each of the two examples in Gokarn Provisional prepared EMAB *with a buffer*. While Gokarn

Provisional attempts to predict by extrapolation the buffer capacity of EMAB in solution, it concedes that "[a] more accurate estimate of the buffer capacity from EMAB alone *will have to be obtained* from bufferless high concentration EMAB solutions." (Ex. 1204, 13.) Gokarn Provisional does not show possession of any such high concentration EMAB solutions without a buffering system. Instead, it states that such investigations were "on-going." (*Id.*)

A vague disclosure of so-called "ongoing" experimentation does not satisfy the written description requirement. *Boston Sci.*, 647 F.3d at 1365-66 (specification describing claimed subject matter as "still under active investigation" provided inadequate written description); *Forty Seven, Inc. v. Stichting Sanquin Bloedvoorziening*, No. IPR2016-01529, Paper 13 at 11 (P.T.A.B. Feb. 9, 2017) (denying petition because the provisional disclosure on which petitioner relied only conveyed "a 'mere wish or plan' for obtaining the claimed invention") (citation omitted).

Gokarn Provisional therefore fails to provide a written description of this additional subject matter Petitioner relies on—the purported disclosure that buffers are unnecessary for all IgG (or IgG1) antibodies at concentrations of 50 mg/ml. (Pet., 36-37.) Accordingly, Gokarn '011 is not entitled to the priority date of Gokarn Provisional.

B. Petitioner Fails To Establish That Gokarn Provisional Supports Claims 162 Or 165 Of Gokarn '011

Petitioner also fails to establish that Gokarn Provisional provides written description support for claims 162 or 165 of Gokarn '011, as it is legally required to do in order to rely on Gokarn Provisional's filing date. For this independent reason, Gokarn '011 is not entitled to the filing date of Gokarn Provisional. *See Dynamic Drinkware, LLC, v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

Claims 162 and 165 of Gokarn '011 recite:

> 162. A pharmaceutical protein formulation comprising: an antibody in an amount sufficient for maintaining pH control; and a pharmaceutically acceptable excipient, wherein said pharmaceutical protein formulation is buffered by said antibody, and wherein the formulation lacks a buffer, apart from the antibody.
>
> 165. The pharmaceutical protein formulation of claim 162, wherein the antibody is epratuzumab.

(Ex. 1203, 37.)

1. Petitioner fails to propose a claim construction for claims 162 or 165

Petitioner acknowledges that for Gokarn Provisional to provide written description support for these claims, the four corners of Gokarn Provisional must disclose to one skilled in the art that the inventor possessed the *claimed* subject matter. (Pet., 25.) But to compare the disclosure of Gokarn Provisional to claims

162 and 165 of Gokarn '011, the Board must first determine the scope of those claims. *X2Y Attenuators, LLC v. ITC*, 757 F.3d 1358, 1365 (Fed. Cir. 2014) (written description analysis requires first construing the claims).

It is apparent from Petitioner's arguments and Dr. Radtke's testimony that the meaning of the phrase "wherein the formulation lacks a buffer" in claims 162 and 165 is important. Their discussions focus on whether Gokarn Provisional discloses "bufferless" or "buffer-free" formulations. (Pet., 26-32; Ex. 1202, ¶¶78-89.) *But neither Petitioner nor Dr. Radtke proposes a construction for the term "wherein the formulation lacks a buffer" or for any other term in claim 162 or 165* of Gokarn '011. *See X2Y Attenuators*, 757 F.3d at 1365. This failure renders Petitioner's and Dr. Radtke's analyses deficient.

2. Claim 162 lacks written description support

Petitioner argues that claim 162 of Gokarn '011 has written description support because it is "similar" to claim 1 of Gokarn Provisional. (Pet., 26.) But claim 1 is broadly directed to preparing pharmaceutical formulations comprising an antibody in an amount sufficient for maintaining pH control and buffering the formulation. (*Id.*; Ex. 1204, 14.) Claim 1 does not include claim 162's language that "the formulation lacks a buffer, apart from the antibody." (Ex. 1204, 14.) It merely recites a broad genus of antibodies defined by their function (*e.g.,* "pH control"), and thus fails to support claim 162. (*Id.*)

Moreover, Petitioner cannot establish written description support by asserting that claim 162 of Gokarn '011 and claim 1 of Gokarn Provisional are "similar." *Ariad*, 598 F.3d at 1349-50 (an original claim may not support written description); *Forty Seven*, IPR2016-01529, Paper 13 at 10-11. Rather, Petitioner must show that Gokarn Provisional provides written description support for the full scope of claim 162. *Id*.

As the Board held in *Forty Seven*: "A sufficient description of a genus . . . requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Id.* at 11 (quoting *Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568-69 (Fed. Cir. 1997)); *see also AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299 (Fed. Cir. 2014). Petitioner does not attempt to meet this test, identifying no representative species and no structural features common to members of the genus.

Instead, Petitioner asserts (1) that "a POSA would have understood that the Gokarn Provisional also describes buffer-free antibody formulations" and (2) "[a] POSA would readily conclude from the disclosure of the Gokarn Provisional that Gokarn was in possession of antibody formulations without a buffer 'apart from the antibody,' as claimed in claim 162 of Gokarn '011 application." (Pet., 27-28.)

The only support Petitioner provides for this statement is paragraphs 90-92 of Dr. Radtke's declaration. (Ex. 1202.) But this testimony is just as conclusory as the Petition. (*Id.,* ¶¶ 90-92; Pet. 27-28.) Such conclusory expert testimony should be accorded no weight. 37 C.F.R. § 42.65(a); *Zimmer Biomet Holdings, Inc. v. Four Mile Bay, LLC*, No. IPR2016-00011, Paper 8 at 11 (P.T.A.B. Apr. 1, 2016); *Johns Manville Corp. v. Knauf Insulation, Inc.*, No. IPR2015-01633, Paper 10 at 13 (P.T.A.B. Jan. 4, 2016).

Both Petitioner and Dr. Radtke allege that Gokarn Provisional includes actual "data" measuring the buffering capacity of EMAB solutions without an "extraneous buffer." (Pet., 27; Ex. 1202, ¶¶ 84-88, 92, 110, 138.) This is incorrect. Gokarn Provisional discloses only two examples, both of which are *buffered*: "Acetate Buffered EMAB" and "Low Succinate Buffered EMAB." (Ex. 1204, 4-5.) Its "Conclusion" states that "[a] more accurate estimate of the buffer capacity from EMAB alone *will have to be obtained* from bufferless high concentration EMAB solutions (*on-going*)." (*Id.*, 13.) Thus, Gokarn Provisional does not show possession of any "bufferless" EMAB solution.

Gokarn Provisional therefore does not provide written description support for claim 162 at least because it does not describe preparing or testing any "bufferless" antibody solution. Instead, it at most describes *an "on-going"*

research plan, which is insufficient. *See Boston Sci.*, 647 F.3d at 1365-66; *Forty Seven*, IPR2015-01529, Paper 13 at 11-13.

3. Claim 165 lacks written description support

Petitioner also asserts that Gokarn Provisional supports dependent claim 165 of Gokarn '011, which specifies that the antibody of claim 162 is EMAB. (Pet., 29.) But, as discussed above, Gokarn Provisional does not describe any "bufferless" EMAB solutions, and Gokarn Provisional's *"on-going" research plan* cannot support claim 165. (Ex. 1204, 13.) S*ee Boston Sci.*, 647 F.3d at 1365-66; *Forty Seven*, IPR2015-01529, Paper 13 at 11-13. Accordingly, Petitioner failed to establish that Gokarn '011 is entitled to claim priority to Gokarn Provisional.

C. The Petition Relies Solely On Priority To Gokarn Provisional

The Petition relies solely on Gokarn Provisional's filing date as the asserted Section 102(e) prior art date, and makes *no attempt* to rely on the filing date of any other application in the priority chain of Gokarn '011. (*See* Pet., §§ IX(C), X, XII.) And the Petition does not identify any disclosure in any later application that would provide written description support for its obviousness allegations. (*Id*.) Because the Petition fails to establish priority to Gokarn Provisional or rely on any other filing date, Petitioner has not shown that Gokarn '011 qualifies as a prior art reference before its 35 U.S.C. § 371(c) date of July 19, 2016. *Dynamic Drinkware*, 800 F.3d at 1381-82. The '619 patent was filed before that date and issued on July

21, 2015. (Ex. 1201.) Because Petitioner has not shown that Gokarn '011 qualifies as prior art to the '619 patent, the Petition should be denied.[4]

VI. The Challenged Claims Would Not Have Been Obvious Over The HUMIRA Label In View Of Fransson And Gokarn '011

Petitioner contends that it would have been obvious to achieve the claimed adalimumab formulation without a buffering system because a skilled artisan allegedly would have been motivated to remove the citrate-phosphate buffering system from the highly successful HUMIRA formulation to avoid injection pain and eliminate "unnecessary excipients." (Pet., 37-43.) Petitioner further contends that a skilled artisan would have had a reasonable expectation of success in arriving at the claimed formulations. (Pet., 44-50.) These theories, however, are unsupported by the cited references and tainted by hindsight reasoning. Petitioner therefore fails to establish a reasonable likelihood that the challenged claims are unpatentable as obvious.

[4] Petitioner is not entitled to any intermediate filing date. If Petitioner intended to rely on additional disclosure from other applications not contained in Gokarn Provisional, it was required to explain its theory in the Petition such that Patent Owner could respond. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016); 35 U.S.C. § 312(a)(3); 37 C.F.R. § 42.22(a)(2).

A. Petitioner Fails To Establish Any Motivation To Remove HUMIRA's Buffering System

1. Petitioner does not establish that injection site pain would have motivated one of ordinary skill in the art to eliminate the buffering system from HUMIRA

Although Petitioner asserts that the "self-buffering" capabilities of proteins were known "for decades" (Pet., 14), as of 2007, *all* commercially available aqueous monoclonal antibody pharmaceutical formulations were provided with a buffering system. (Ex. 1286, 2-4; *see also* Ex. 2055, 852.). The same held true as late as 2015. (Ex. 2051, 94-101 (Table 4.1); *see also* Ex. 2055, 852.)

HUMIRA, for example, was initially approved in 2002 and was successfully formulated with a multi-component citrate-phosphate buffering system. (Ex. 1286, 2; *see also* Ex. 1205, 470.) Indeed, at the time of the '619 patent invention, this groundbreaking buffered formulation was the only approved monoclonal antibody formulation intended for subcutaneous injection that was not lyophilized, meaning that it could be administered directly without reconstitution. (*See, e.g.,* Ex. 1286, 2-4.)

Petitioner nevertheless alleges that one would have been motivated to eliminate HUMIRA's buffering system because the HUMIRA Label discloses that 12% of patients in clinical trials reported injection site pain. (Ex. 1205, 472.) Petitioner further alleges that this injection site pain caused "compliance issues." (Pet., 39.) The HUMIRA Label, however, does not identify injection site pain as an

adverse event leading to discontinuation. (Ex. 1205, 472.) Rather, it states that the most common adverse events leading to discontinuation were clinical flare reaction (0.7%), rash (0.3%), and pneumonia (0.3%). (*Id*.)

Petitioner's declarant, Dr. Sherry, cites no documentary evidence of compliance issues for HUMIRA resulting from injection site pain. (Ex. 1207, ¶¶21-23 (basing opinions on what he "heard" about the "patient experience," rather than any published literature).) The Board should disregard this unsupported testimony. 37 C.F.R. § 42.65(a) (unsupported testimony is entitled to "little or no weight"); *see also TRW Auto. US LLC v. Magna Elecs., Inc.,* No. IPR2014-00258, Paper 18 at 11 (P.T.A.B. Aug. 27, 2014) (the Board has "well-established discretion to give little weight to conclusory, unsupported expert testimony"). Indeed, Petitioner offers no tangible evidence that injection site pain affected patient use of HUMIRA, one of the most successful drug products of all time. (Ex. 2042, 1.)

Accordingly, Petitioner's assertion that injection site pain would have motivated one of ordinary skill in the art to modify the highly successful HUMIRA formulation is without merit.

a. Petitioner ignores the multitude of other factors that contribute to injection site pain.

Even *if* pain injection site pain was a perceived problem, contrary to Petitioner's conclusory assertion, a skilled artisan had far more than "[a]t most" two predictable solutions available to reduce such pain (*i.e.,* selecting a different buffering system or eliminating the buffering system entirely) (Pet., 41). Instead, a skilled artisan would have been aware of the multitude of potential contributors to injection site pain, and the numerous potential avenues to address each one.

Fransson, for example, discloses several causes of injection pain, including injection volume, injection speed, osmolality, pH, injection site, needle size, needle quality, presence of irritating substances, and temperature. (Ex. 1219, 1012.) Brazeau 1998 lists twenty injection-pain factors, which were "by no means inclusive." (Ex. 2003, 672-73.) In fact, the art described many possible causes of injection site pain, including:

i. Intrinsic properties of the active ingredient. (Ex. 2003, 673.)

ii. High concentrations of the active ingredient. (*Id.*)

iii. Protein aggregation. (*Id.*)

iv. Greater formulation viscosity. (Ex. 2009, 1929.)

v. pH. (Ex. 1219, 1012; Ex. 1201, 218; Ex. 2049, 585; Ex. 2002, 730.)

vi. Anatomical site of injection. (Ex. 2008, 679; Ex. 1219, 1012.)

vii. Temperature at injection site. (Ex. 2005, 57; Ex. 1219, 1012.)

viii. Injection volume. (Ex. 2002, 730; Ex 1219, 1012.)

ix. Injection technique. (Ex. 2003, 673.)

x. Speed and rate of injection. (*Id.*)

xi. Needle size and length. (Ex. 2006, 179; Ex. 1219, 1012.)

xii. Tonicity. (Ex. 2003, 673.)

xiii. Buffer concentration. (Ex. 1219, 1014.)

xiv. Preservatives. (Ex. 2002, 730.)

xv. Osmolality. (*Id.*; Ex. 1219, 1012.)

xvi. Osmolarity. (Ex. 2003, 673.)

xvii. Frequency of injection. (Ex. 1201, 218.)

xviii. Individual patient characteristics. (*Id.*)

Petitioner disregards these other known causes of injection site pain. Petitioner also ignores known effective, low-tech solutions for reducing injection pain such as applying ice to the skin. (Ex. 2005, 57 (applying ice to the skin before injection "decreases the pain perception considerably").)

Petitioner's selective focus on the buffering system of HUMIRA reflects hindsight bias and an improper obvious-to-try rationale. Where, as here, the prior art does not indicate which parameters are critical or which of many possible choices would likely succeed, an invention is not obvious to try. *Unigene Labs.,*

Inc. v. Apotex, Inc., 655 F.3d 1352, 1361 (Fed. Cir. 2011); *see also BioDelivery Scis. Int'l, Inc. v. MonoSol Rx, LLC*, No. IPR2015-00167, Paper 6 at 19-20 (P.T.A.B. May 20, 2015) (denying institution of ground where prior art merely suggested varying all parameters or trying each of numerous possible choices until possibly arriving at successful result).

b. Fransson does not suggest removing a buffering system

Notwithstanding the numerous recognized causes of injection site pain, Petitioner asserts that the citrate-phosphate buffer in HUMIRA was "the most likely cause" of injection site pain reported in the HUMIRA Label. (Pet. 39-41). Petitioner relies on Fransson's disclosure that "citrate buffer causes pain" (*see, e.g.,* Pet., 39 (*citing* Ex. 1219,1012)) as allegedly motivating a skilled artisan to remove HUMIRA's entire buffering system to alleviate this pain. (*Id.*, 39-43).

As an initial matter, Fransson was published in 1996, more than a decade before the 2007 priority date of the '619 patent. Fransson does not disclose or concern *any* antibody, much less HUMIRA, but is instead directed to solutions of a globular protein (hIGF1). (Ex. 1219, 1012.)

Moreover, Fransson does not disclose omitting a buffering system or describe any formulation without a buffering system, which Petitioner fails to acknowledge. (*See* Pet., 36.) Rather, each of the eight solutions Fransson tested

contained phosphate buffer in varying concentrations. (Ex. 1219, 1012.) Petitioner attempts to read more into Fransson than it actually discloses, using the challenged claims as a template to reconstruct the invention with improper hindsight. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) (reversing obviousness determination as improperly based on hindsight). Fransson cannot motivate what it does not disclose. *Redline Detection, LLC v. Star Envirotech, Inc.*, 811 F.3d 435, 453 (Fed. Cir. 2015) (affirming nonobviousness because one would not have looked to a reference teaching use of an inert gas to modify another reference requiring the presence of oxygen).

Instead of removing a buffer, Fransson *uses a buffer* (specifically, sodium phosphate) in *all* of its disclosed solutions. (Ex. 1219, 1012-13.) Petitioner's focus on Fransson's limited discussion of citrate buffers ignores Fransson's express endorsement of sodium phosphate, one of the buffers used in HUMIRA. (Ex. 1205, 470.) Petitioner does not (and cannot) explain why Fransson would have motivated one of ordinary skill in the art to *remove* the very buffer that Fransson *used*. Moreover, Fransson's mention of pain caused by a *citrate* buffer does not suggest any motivation to entirely remove the two-component (*phosphate and citrate*) buffering system from AbbVie's highly successful, FDA-approved HUMIRA product.

Petitioner argues that Fransson's suggestion to keep buffer strength "*as low as possible*" suggests eliminating HUMIRA's buffering system. (Pet., 40 (emphasis in original).) But Fransson's disclosure does not support this assertion. Fransson discloses that an intermediate buffer concentration (10 mM) minimizes injection pain, and that *continuing to lower the concentration provides no further benefit*. (Ex. 1219, 1012-14 (reporting decreased injection pain when lowering buffer concentration from 50 mM to 10 mM, but no further reduction in pain when further lowering buffer concentration to 5 mM).) Fransson's disclosure that no additional benefit is achieved when reducing phosphate buffer concentration below a particular threshold refutes any alleged motivation to *eliminate* HUMIRA's citrate-phosphate buffering system.

Petitioner does not even establish that Fransson would have motivated one to *reduce* the phosphate component of HUMIRA's buffering system. Petitioner does not evaluate how HUMIRA's citrate-phosphate buffering system compares with the 50 mM, 10 mM, or 5 mM sodium phosphate buffer concentrations in the Fransson solutions. Thus, Petitioner does not demonstrate that Fransson would have guided or motivated one to reduce the phosphate concentration of HUMIRA's buffering system, much less remove the entire citrate-phosphate buffering system altogether.

c. Other buffering systems were not known to be associated with injection site pain

Petitioner also does not establish that one of ordinary skill in the art would have eliminated the citrate-phosphate buffering system of HUMIRA instead of choosing a different buffering system. As discussed above, for example, Fransson proposed substituting a phosphate buffering system—*i.e.,* one of the buffer components of HUMIRA—instead of a citrate buffering system. (Ex. 1219, 1012.) Other studies similarly advised replacing citrate buffer with phosphate buffer to reduce pain. (*See, e.g.,* Ex. 1217, 299; Ex. 1221, 218; Ex. 2011, 41; Ex. 2012, 341.) Histidine, a known alternative to citrate buffers, was associated with no pain on injection. (*See, e.g.,* Ex. 1217, 299; Ex. 1221, 218.) Gokarn Provisional disclosed acetate- or succinate-buffered EMAB solutions, rather than eliminating buffer. (Ex. 1204, 4-5.)

In addition to suggesting buffer *substitution* instead of *removal*, the literature downplayed the connection between buffering systems and injection site pain. For example, while comparing citrate- and phosphate-buffered epoetin-alpha (EPO) solutions, Veys *et al.* noted the limitations of adjusting buffer systems to address pain: "the presence of citrate . . . is not the only culprit of local discomfort." (Ex. 2011, 44.) Accordingly, the scientific literature does not support Petitioner's heavy

reliance on alleged buffer-related injection pain to justify eliminating the buffering system from the highly successful HUMIRA formulation.

Notably, Petitioner's own declarant admits that subcutaneous injections of phosphate-buffered protein preparation were "rarely described as being particularly painful" and instead were "largely attributed to the injection itself (*i.e.*, the needle stick)." (Ex. 1207, ¶26.)

d. "Buffer-free" formulations cited by Petitioner cause injection site pain

Petitioner contends that commercially available human plasma-derived immunoglobulin products were formulated at high concentrations without a separate buffering system. (*See, e.g.,* Pet., 16; Ex. 1202, ¶¶47-48 (citing Exs. 1225, 1226, 1254-1261).) As an initial matter, Petitioner does not show that any of these products are similar to HUMIRA. None of them is a monoclonal antibody product like HUMIRA, and HUMIRA is administered by subcutaneous injection (Ex. 1205, 470) whereas the cited products are generally administered using either intramuscular injections or, more commonly, lengthy intravenous infusions. (*See, e.g.,* Ex. 1225, 925, 928; Ex. 1226, 558, 805, 914-919; Ex. 1256, 1; Ex. 1259, 872.)

Moreover, the labels for these allegedly "buffer-free" products describe *pain on injection* and other injection site reactions. The NABI-HB label, for example, reported that 12% of patients had local pain associated with administration—the

same percentage as HUMIRA. (Ex. 1226, 2296; Ex. 1205, 472.) IMOGAM RABIES had "*tenderness, pain, soreness* or stiffness of the muscles [that] may occur at the injection site." (Ex. 1226, 806.); *see also* VIVAGLOBIN (Ex. 1254, 7 (reporting that 92% of subjects had "adverse events at the injection site")); RHOGAM (Ex. 1226, 2524 ("swelling, induration, redness and mild *pain* at the site of injection")); BAYGAM (*Id*., 915 ("*pain and tenderness* at the injection site")); BAYHEP B (*Id*., 916 ("*pain and tenderness* at the injection site")); BAYRAB (*Id*., 918 ("*[s]oreness* at the site of injection")); BAYRHO-D (*Id*., 922 ("*soreness* at the site of injection")); BAYTET (*Id*., 924 ("*soreness* at the site of injection")); and GAMMAGARD LIQUID (Ex. 1256, 3 (indicating that infusion site events occurred in 13.1% of the subjects).)

Petitioner does not explain why one of ordinary skill would have removed the buffering system of HUMIRA instead of pursuing the plethora of possible ways to address injection site pain, particularly when these allegedly "buffer-free" commercial products failed to solve the alleged problem of injection site pain.

2. Petitioner fails to show that regulatory or processing cost concerns would have motivated one skilled in the art to remove HUMIRA's buffering system

Petitioner asserts that regulatory authorities "expect exclusion of unnecessary excipients." (Pet., 42.) Petitioner fails to prove, however, that this would have motivated one skilled in the art to remove any particular excipient—

much less the buffering system—from the *FDA-approved* and highly successful formulation of HUMIRA. (Ex. 1209, 1, 3.) Consistent with the Gokarn textbook chapter quoted by Petitioner (Pet., 42), the safety and tolerability of HUMIRA's buffered formulation was already established through development studies, resulting in its FDA approval. (*See* Ex. 1209, 1-3.) As discussed in Section VI.B.4 below, Petitioner fails to prove that HUMIRA's buffering system was "unnecessary" or "extraneous" (Pet. 33) such that one would have been motivated to remove it. (*See also, e.g., infra* Section VI.A.3.) Indeed, given this alleged expectation that only appropriate excipients will be included, the FDA's approval of HUMIRA as a buffered formulation suggests that a buffering system was viewed as "essential in imparting a desired pharmaceutical effect (*i.e.,* stability or delivery)." (Pet. 42, (quoting Ex. 1217, 294-95).) Petitioner's argument is also contradicted by the regulatory approval of dozens of other liquid monoclonal antibody products in *buffered* solutions. (Ex. 2051, 94-101 (Table 4.1); *see also* Ex. 2055, 852.)

Petitioner also argues that eliminating HUMIRA's buffering system would "simplify manufacturing and quality control processes." (Pet., 43.) The Petition does not cite any evidence, however, concerning HUMIRA's manufacturing or quality control processes. (Pet., 43; *see also* Ex. 1202, ¶¶54-55, 105.) Dr. Radtke's assertions regarding "cost savings" are not specific to HUMIRA and should

therefore be disregarded as conclusory and unsupported. (Ex. 1202, ¶¶55, 105); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) (a lack of objective support for expert opinion may render the testimony of little probative value). Petitioner and Dr. Radtke also fail to account for the processing controls and manufacturing steps required to prepare a formulation *without a buffering system*. (Pet., 43; *see also* Ex. 1202, ¶¶54-55, 105.) Thus, Petitioner's "cost savings" position is unsupported and hindsight-driven. *See, e.g., Leo Pharm.*, 726 F.3d at 1354.

Petitioner therefore has not proven that any regulatory or processing cost concerns would have motivated one of ordinary skill to remove the buffering system of HUMIRA.

3. Petitioner previously argued that one of ordinary skill would have included a buffer with adalimumab

Petitioner's arguments concerning the purported motivation to eliminate buffers from HUMIRA are also contradicted by its own prior arguments to the Board. In a previous IPR Petition, Petitioner asserted that buffers *should be included* in formulations of adalimumab because they maintain the solution pH and affect stability of the antibody. *See*, *e.g., Coherus Biosciences Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2016-01018 ("*Coherus* IPR"), Paper 1 at 33 (P.T.A.B. May 9, 2016) ("A POSA would have been motivated to prepare a stable liquid

formulation of [adalimumab] *with a buffer system* . . . .".). Petitioner's expert in that proceeding testified, for example, that adalimumab should be formulated with a buffer because buffered formulations were the "standard in the industry." (Ex. 2004, ¶64.) He specifically identified citrate and phosphate buffer systems, used in other commercial products, as useful and appropriate. (*Id.*, ¶143.) And he testified that it "was a given" that an adalimumab formulation should include a buffer. (*Id.*, ¶156; *see also id.*, ¶¶103, 107, 149, 156, 166, 170.)

And while Petitioner now attempts to retreat from its previous representations to the Board in support of aqueous adalimumab formulations that *include a buffering system*, such as a citrate or phosphate buffering system, Petitioner itself continues to pursue *at least a dozen* patents and patent applications—filed in 2012, almost *five years after* the priority date of the '619 patent—having claims directed to *buffered* adalimumab formulations. (*See, e.g.,* U.S. Pat. Nos. 9,340,611; 9,340,612; 9,346,880; and U.S. Pat. Pub. Nos. 2014/0186361; 2015/0190513; 2016/0039926; 2016/0031982; 2016/0256545; 2016/0256546; 2016/0256547; 2016/0263226; 2017/0072054.) This includes pursuing claims directed to adalimumab formulations that are specifically *phosphate*-buffered (*see, e.g.,* U.S. Pat. Pub. No. 2016/0039926 and 2016/0031982) or *citrate*-buffered (*see, e.g.,* U.S. Pat. Pub. No. 2016/0031982).

Accordingly, Petitioner fails to establish that HUMIRA's injection site pain would have motivated a skilled artisan to entirely remove the buffering system from HUMIRA. For at least this reason alone, institution should be denied.

B. Petitioner Fails To Demonstrate A Reasonable Expectation Of Successfully Formulating Adalimumab Without A Buffering System

Petitioner also fails to establish that one of ordinary skill would have had any reasonable expectation of success of obtaining an aqueous adalimumab pharmaceutical formulation at a concentration of 50-200 mg/ml without a buffering system, as claimed in the '619 patent.

1. Gokarn Provisional's EMAB examples provide no reasonable expectation of successfully preparing the claimed adalimumab formulations

Petitioner alleges that one of ordinary skill would have had a reasonable expectation of success in obtaining the claimed adalimumab formulations based on the teachings of Gokarn Provisional. (Pet., 44.) Petitioner relies on Gokarn Provisional's data for one antibody, EMAB, and asserts that "demonstration of buffering capacity for EMAB also would apply to adalimumab." (Pet., 45, 47.) These EMAB examples are insufficient, however, to establish any reasonable expectation of success in achieving the claimed adalimumab formulations.

Gokarn Provisional does not disclose adalimumab at all. Instead, it discloses results from only a single antibody, EMAB. (Ex. 1204, 4-5.) But, it does not

describe the structure of EMAB. Nor does Petitioner contend that EMAB and adalimumab are the same, which they are not.

Gokarn Provisional's only examples each formulate EMAB *in a buffering system* and at a concentration *lower* that 50 mg/ml. (*Id.*) In the first example, EMAB was concentrated to a maximum of only 46 mg/ml in *acetate buffer*, at which point the solution became "cloudy." (*Id.*, 4.) In the second example, EMAB was concentrated to a maximum of only 45 mg/ml in a *succinate buffer*, at which point "cloudiness appear[ed]." (*Id.*, 5.) Gokarn Provisional does not disclose (i) any antibody formulation without a buffering system, or (ii) any antibody formulation that reached a concentration of 50 mg/ml. Rather, it evidences a *failure* by applicants of Gokarn Provisional to achieve a 50 mg/ml concentration in even a single disclosed antibody solution, as demonstrated by the cloudiness observed in each of the two exemplified EMAB preparations. (*Id.*, 4-5.)

Gokarn Provisional attempts to predict by extrapolation the buffering capacity of EMAB in solution, while conceding that "[a] more accurate estimate of the buffer capacity from EMAB alone *will have to be obtained from bufferless high concentration EMAB solutions*." (*Id.*, 13.) But it does not show possession of any such "bufferless," high concentration EMAB solutions. Instead, Gokarn Provisional states that such investigations were "on-going." (*Id.*) This disclosure of continuing research does not prove a reasonable expectation of successfully

achieving a high concentration antibody formulation without a buffering system, much less one for adalimumab. *Alza Corp v. Mylan Labs., Inc.*, 464 F.3d 1286, 1290 (Fed. Cir. 2006) (obviousness should be based on evidence, not speculation or conjecture); *see Star Sci., Inc. v. R.J. Reynolds Tobacco Co.,* 655 F.3d 1364, 1375-76 (Fed. Cir. 2011) (prior art's tentative disclosure of what might cause a result does not "sufficiently direct or instruct" one of ordinary skill in the art).

Gokarn Provisional offers no evidence that an aqueous solution of *any* antibody was (or can be) prepared without a buffering system. Thus, any attempts to extend the data in Gokarn Provisional—for an unrelated antibody, in a buffered solution, at a concentration below that which is claimed—to adalimumab at a high concentration without a buffering system are without merit.

Petitioner admitted as much to this Office during prosecution of its own patent portfolio. In prosecuting a patent application directed to formulations of adalimumab filed in 2012, *nearly five years after* the earliest priority date of the '619 patent, Petitioner recently argued that a publication directed to formulations of different (non-adalimumab) antibodies did not apply to its claimed formulations of adalimumab:

> [WO 1996/056418 to Lam] is not directed to adalimumab formulations, nor does it even mention adalimumab . . . . *Since WO '418 discloses different formulations for different antibodies, it*

> *does not support the Office Action conclusion "the antibody formulation of the '418 publication is suitable for any antibodies."*

Ex. 2043, 5; *see also* Ex. 2044, 3-4; Ex. 2045, 6 ("Zolton teaches immunoglobulins in general, which would not lead [one of ordinary skill in the art] to combine the teachings of Zolton with those" relating to adalimumab.).)

Petitioner's representations to the Office contradict its position here, and Petitioner cannot have it both ways. Gokarn Provisional discloses different solutions for a different antibody at concentrations below that which are claimed. Therefore, it does not support Petitioner's assertion that one skilled in the art would have had a reasonable expectation of success in arriving at the claimed high-concentration adalimumab formulations that do not comprise a buffering system.

2. A formulation designed for one antibody would not have been expected to apply to a different antibody

Petitioner also asserts that one of ordinary skill in the art would have reasonably expected success in removing the buffering system from HUMIRA because Gokarn Provisional states that antibodies in general "have sufficient buffering capacity to be formulated without extraneous buffers." (Pet., 44.) Petitioner further argues that a skilled artisan would have understood Gokarn Provisional's demonstration of buffering capacity for EMAB to apply to adalimumab. (Pet., 47.) Petitioner, however, does not discuss the unpredictability in applying a formulation from one antibody to another or establish that antibodies

of similar class or sequence would have been expected to have the same buffer capacity.

Indeed, in 2007, there was general consensus in the art that a formulation that worked for one antibody (such as EMAB) would *not* be predicted to work for a different antibody (such as adalimumab). For example, the Wang 2007 review article (Ex. 1286) explained the complexities associated with formulating different antibodies:

> Development of commercially viable antibody pharmaceuticals has, however, not been straightforward. This is because the behavior of antibodies seems to vary, even though they have similar structures.

(*Id.*, 5.)

Rather, Wang and others explained that each antibody had to be evaluated *individually* when developing a liquid formulation because of their differing structures and properties. (*See id.*, 21.) Persons skilled in the art rejected the notion that a formulation useful for one antibody could reasonably be expected to be successfully applied to other similar antibodies. (Ex. 2021, 690 (each IgG1 antibody "seems to have a unique personality related to its requirements for stability" arising from even small differences in protein folding and solvent-exposed amino acid residues).) Therefore, the assumptions by Petitioner and its declarant that a "high degree of identity" among amino acid sequences in IgG antibodies would lead to similar buffering capacities and formulation requirements

are unsupported. (Pet., 47-48; Ex. 1202, ¶¶33-37); 37 C.F.R. § 42.65(a); (Ex. 2028, 271 (reporting in 2014 that "[d]espite recent advances, the identification of suitable formulation conditions for a specific monoclonal antibody remains challenging and *cannot be determined from its amino acid sequence*").) Rather, different proteins need to be evaluated individually using only trial-and-error. (*See, e.g.,* Ex. 2001, 130.) Indeed, Petitioner's argument is contradicted by Gokarn '011, which concedes that buffering capacities of a protein's amino acid residues "can vary dramatically" due to protein folding, and concludes that empirical experimentation is "a crucial aspect of formulating self-buffering compositions." (Ex. 1203, [0209], [0206].)

Accordingly, to produce a formulation for a particular antibody, one had to identify the appropriate ionic strength, pH, and buffer type so as to minimize precipitation and other adverse events (*e.g.*, deamidation). (Ex. 2016, 1333.) Yet even a skilled artisan's "best efforts" at developing antibody formulations were unpredictable and not reasonably expected to succeed, as a result of inherent limitations of antibodies themselves. (Ex. 2021, 701.) Even as recently as 2014, the scientific literature reported the use of buffering systems, such as citrate, to produce a successful formulation. (Ex. 2028, 271.)

Moreover, it was well known that liquid monoclonal antibody formulations suffered from problems such as aggregation, which were more likely to occur as

the antibody concentration increased. (*See*, *e.g.,* Ex. 1286, 9 ("Increasing the concentration of antibodies often increases the aggregation tendency of the protein."); Ex. 2009, 1929; Ex. 2021, 693; Ex. 2001, 152.) Similar problems continued to be reported after the priority date. (*See*, *e.g.,* Ex. 2025, 6109 ("increasing immunoglobulin (IgG) concentration increases self association of these molecules").) Petitioner does not provide any evidence regarding the properties of adalimumab or any analysis of the aggregation tendencies of adalimumab in a formulation without a buffering system. Instead, Petitioner overgeneralizes and merely alleges that one of ordinary skill knew "for decades" that proteins could be "self-buffering" at high concentrations. (Pet., 14.) Petitioner therefore does not establish any reasonable expectation of success in obtaining an adalimumab formulation without a buffering system at 50 mg/ml.

Petitioner also attempts to distinguish the Board's earlier decision in IPR2016-01018, which recognized that a formulation for one antibody would not have reasonably been expected to succeed for a different antibody, adalimumab. (Pet., 51-54.) *Coherus* IPR, Paper 10 (Decision Denying Institution) (P.T.A.B. Nov. 7, 2016); *Coherus* IPR, Paper 12 (Decision Denying Request for Rehearing) (P.T.A.B. Feb. 2, 2017). Petitioner argues that the state of the art in the earlier *Coherus* IPR was "very different" because the challenged patent was effectively filed in 2002, five years before the '619 patent's 2007 priority date. (Pet., 51-52.)

In denying Coherus's Request for Rehearing, however, the Board relied on the same Wang 2007 reference discussed above, which is contemporaneous with the filing of the '619 patent. The Board concluded:

> Wang 2007 also states that "development of commercially viable antibody pharmaceuticals has, however, not been straight forward. This is because the behavior of antibodies seems to vary, *even though they have similar structures*." Despite acknowledging the similarity in structures, Wang 2007 repeatedly states that the differences among antibody sequences affect the stability of antibody pharmaceuticals . . . . Finally, Wang 2007 concludes that one of the "major issues in antibody formulation that is apparently challenging and needs significant attention in the coming years [includes] development of stable high-concentration formulations." Taken together, we are not persuaded that structural similarity of 95% amongst IgG_1 antibodies necessarily means a person of ordinary skill in the art would have expected all IgG_1 antibodies to behave similarly. Nor, for similar reasons, are we persuaded that Petitioner has shown sufficiently that a person of ordinary skill in the art would have had a reasonable expectation of success in formulating a stable, liquid, high-concentration D2E7 [adalimumab] formulation, as required by the claims.

Coherus IPR, Paper 12 at 3-4 (emphasis in original) (citing Ex. 1286, 5, 14, 21).

Here, Petitioner's proposed obviousness challenge is similar to the one denied in the earlier *Coherus* IPR. Petitioner again purports to make sweeping

inferences about the entire category of IgG antibodies, and then apply those inferences to one specific antibody, adalimumab. (Pet., 53.) Petitioner's reliance on Gokarn Provisional's description of buffered solutions for a different antibody (EMAB) to try to arrive at a formulation for adalimumab similarly runs afoul of the Board's finding in the *Coherus* IPR that one would not have expected all IgG1 antibodies to behave similarly. (*Id.*); *Coherus* IPR, Paper 12 at 3-4. Petitioner's current obviousness challenge merely repackages different theories previously rejected by the Board.

The Board in the *Coherus* IPR was not alone in reaching the conclusion that one would not have had a reasonable expectation of success in attempting to formulate one antibody based on formulations designed for different antibodies. For instance, in IPR2015-01514, the Board denied a petition filed against another AbbVie patent filed in 2002. *Amgen, Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2015-01514, Paper 9 at 15-16 (Decision Denying Institution) (P.T.A.B. Jan. 14, 2016). Citing another Wang article (Ex. 2001) containing similar teachings as Wang 2007, the Board concluded that petitioner failed to establish a reasonable expectation of success because, among other things, "structural differences among different proteins are so significant that generalization of universal stabilization strategies has not been successful." *Id.* at 15 (quoting Ex. 2001, 130); *id.* ("Wang suggests a high degree of *un*predictability in the antibody formulation art."); *see*

also Amgen, Inc. v. AbbVie Biotechnology Ltd., No. IPR2015-01517, Paper 9 at 16-17 (Decision Denying Institution) (P.T.A.B. Jan. 14, 2016).

Thus, as discussed above, the scientific literature before and after the '619 patent's 2007 filing date was replete with evidence showing that a formulation designed for one antibody could not be reasonably be expected to be successfully applied to a different antibody. The Board has acknowledged this fact in at least three IPR decisions denying institution.

3. Petitioner fails to establish that all IgG antibodies have "highly similar" buffering capacities

Petitioner alleges that the total number of contributing charged amino acid residues that create buffering capacity is relatively constant for a given class of monoclonal antibodies. (Pet., 45.) Petitioner further alleges that Gokarn Provisional teaches that different antibodies within the IgG class would have similar buffering capacity because of amino acid sequences and tertiary structures across all IgG antibodies are "highly similar." (Pet., 47.) But the contemporaneous scientific literature contradicts these assertions.

Petitioner focuses on the similarity among the constant regions of human IgG antibodies, while omitting the contribution to buffer capacity of the variable regions. (*Id*., 10.) Yet the variable regions make up a substantial portion of the antibody and contain the most sequence diversity. (*See* Ex. 1286, 5 ("The variable

(V) regions of both chains cover approximately the first 110 amino acids, forming the antigen-binding (Fab) regions . . . . The N-terminal sequences of both the heavy and light chains vary greatly between different antibodies.").)

Because the buffering capacity of any particular antibody is mainly attributed to its solvent-exposed amino acid residues, differences in amino acid sequences, particularly in the binding regions, are important. (Ex. 2041, 3062.) As explained in Gokarn '011, this is one of the reasons empirical measurements of protein buffer capacities are preferred. (Ex. 1203, [0200] ("[A] complete description of the hydrogen ion equilibria of a protein in a given environment is beyond the reach of current theoretical and computational methods. Empirical measurements of protein buffer capacities, thus are preferred.").) Petitioner ignores these differences in solvent-exposed residues and thus fails to establish that one skilled in the art would have expected different antibodies within the IgG class to have similar buffering capacities.

Petitioner also fails to account for any structural differences between the exemplified EMAB antibody in Gokarn Provisional and adalimumab, much less those that could affect key properties of the antibody in an aqueous formulation. By the time of the invention, it was known that small changes in antibody amino acid sequence could significantly affect a given formulation. (*See, e.g.,* Ex. 1286, 14, 15, 21 ("Due to the significant difference in the primary sequence among

different antibodies, the relative severity of [] degradation pathways can be significantly different."); *see also* Ex. 2027, 2079.) A 2006 article stated that because of differences in amino acid sequences, the interfacial surface of each antibody drug is unique, meaning that formulations for one antibody cannot reasonably be expected to be successfully applied to other antibodies. (Ex. 2021, 690.) As explained in Wang 2007, an excipient suitable for one antibody may not be suitable for another because of differences in their sequences. (*See, e.g.,* Ex. 1286, 14, 21; Ex. 2028, 271.)

For at least these reasons, one of ordinary skill in the art would not have had a reasonable expectation of success in obtaining the claimed adalimumab formulations without a buffering system based on Gokarn Provisional's formulation of EMAB antibodies.

4. Petitioner fails to address the potential consequences of removing HUMIRA's buffering system

Petitioner argues that it was desirable to remove "unnecessary excipients," relying on Gokarn Provisional for the proposition that a buffering system would be unnecessary for HUMIRA, which was formulated at 50 mg/ml. (Pet. 42-43.) However, as discussed above, Gokarn Provisional is silent as to adalimumab, and its only exemplified antibody (EMAB) could not even be formulated higher than

46 mg/ml in a *buffered* solution. Moreover, Petitioner does not address the consequences of eliminating HUMIRA's buffering system.

Contrary to Petitioner's allegations (*see, e.g.,* Pet., 11), buffers were known to affect protein formulations in ways beyond simply maintaining pH. (*See*, *e.g*., Ex. 2009, 1939 ("[U]nusually high viscosity [results from] concentrated monoclonal antibody in low ionic strength buffers" that can have "a major impact on important pharmaceutical properties.").) Indeed, removing a buffering system from a protein formulation could change the chemistry, stability, and physical characteristics of the overall formulation. (*See*, *e.g*., Ex. 2033, 9690-91; Ex. 2034, 420, 422; Ex. 2035, E3; Ex. 2036, 1581; Ex. 2038, 9871.) *See Nichia Corp. v. Everlight Ams., Inc.*, Nos. 2016-1585/-1618, 2017 WL 1521595, at *7 (Fed. Cir. Apr. 28, 2017) (affirming nonobviousness where "artisans in this field face myriad design challenges because small design changes may cause unpredictable results and because design considerations often pull in multiple directions"). For example, "there are cases where conditions that minimize chemical degradation foster physical damage and vice versa." (Ex. 2039, 969 *see also, e.g.*, Ex. 2013, 110 ("[S]ometimes there are conflicting conditions (e.g., pH) needed to slow sufficiently multiple degradation pathways in aqueous solution."); Ex. 2001, 164.)

Only with improper hindsight, therefore, could there be any reasonable expectation of success. A skilled artisan would not have reasonably predicted the

effects of eliminating the buffering system from the HUMIRA formulation, which could negatively affect the overall formulation (*e.g.*, cause aggregation or cloudiness). Thus, Petitioner has not established a reasonable expectation of success in achieving an aqueous adalimumab formulation that does not comprise a buffering system.

5. The cited references do not disclose adalimumab's buffer capacity

Petitioner and its declarant assert that one of ordinary skill would have concluded from Gokarn Provisional and the HUMIRA Label that 50 mg/ml of adalimumab without an additional buffer could maintain pH of 5.2 during storage. (Pet., 49 (citing Ex. 1202, ¶¶118-20).) This assertion is unsupported, especially because the cited references do not calculate or otherwise determine the buffer capacity of adalimumab. 37 C.F.R. § 42.65(a).

Gokarn Provisional states that the buffering capacity of a protein depends on the number of charged amino acid residues and the total concentration of the protein. (Ex. 1204, 2:18-6:1 (to potentially "self-buffer," a protein must contain "high enough levels" of charged amino acid residues).) Gokarn Provisional, however, does not provide any analysis of the charged amino acid residues present in EMAB or in any other protein. Thus, despite emphasizing the importance of charged amino acid residues, Gokarn Provisional provides no guidance about the

residues present in adalimumab. (*See id.*) Nor does Petitioner argue that such information was known or obtainable by a skilled artisan at the time of the invention.

Gokarn Provisional also does not describe any means for calculating theoretical buffer capacity values for any protein. Instead, Gokarn Provisional shows only empirical estimates of buffer capacity. (*Id.*, 8-12.) It analyzes the acetate- and succinate-buffered solutions of EMAB, comparing them to buffering standards. (*Id.*) Yet Gokarn Provisional concludes that a "more accurate estimate" of EMAB's buffer capacity must be obtained from "bufferless" EMAB solutions not yet developed. (*Id.*, 13 (stating that "bufferless" formulation attempts were "on-going").) Gokarn Provisional therefore illustrates that a protein's buffer capacity must be *empirically* determined, and that even the EMAB-related experimentation disclosed in Gokarn Provisional was not sufficient to determine EMAB's buffer capacity. (*Id.*) Petitioner thus fails to establish that one would have been motivated to draw any conclusions about adalimumab based on Gokarn Provisional's description of EMAB.

Even as late as 2008, a publication by Gokarn acknowledged that a skilled artisan would have understood that buffering capacity of a protein is difficult to predict and determined by multiple factors. (Ex. 2041, 3062.) This reference states

that predicting an antibody's buffering capacity is *nontrivial* and extremely resource-intensive. (*Id*.)

Despite Gokarn Provisional's emphasis on the need to empirically determining a protein's buffer capacity when developing a "self-buffering" protein formulation, it does not identify (or even estimate) the buffer capacity of adalimumab. Nor does Petitioner argue that such information was known or obtainable by a skilled artisan at the time of the invention. Petitioner similarly fails to establish that a skilled artisan would have expected the buffer capacity to be high enough for adalimumab to "self-buffer" at the claimed concentrations. (Ex. 1204, 13 (stating that even for EMAB, a "more accurate estimate" of buffer capacity required additional experimentation).) Petitioner's assertion that one of ordinary skill would have expected adalimumab to "self-buffer" is therefore unsupported and should be disregarded. 37 C.F.R. § 42.65(a).

Finally, even if one of ordinary skill in the art could determine a protein's buffer capacity, that does not mean that one would arrive at an antibody concentration of 50-200 mg/ml. For example, while Gokarn Provisional discloses an attempt to predict by extrapolation EMAB's buffer capacity, the actual EMAB solutions became cloudy at concentrations less than 50 mg/ml. (Ex. 1204, 4-5.) Neither Petitioner nor its declarants address the inability to formulate this monoclonal antibody at a concentration higher than 46 mg/ml.

Because Petitioner failed to prove any motivation to remove HUMIRA's buffering system, much less the requisite evidence to support its claim that one skilled in the art would have had a reasonable expectation of success in doing so, Ground 1 of the Petition should not be instituted.

VII. Ground 2: The Challenged Claims Are Not Obvious Over Gokarn '011 In View Of The HUMIRA Label

Petitioner has challenged claims 16-19 and 24-30 of the '619 patent as allegedly obvious over Gokarn '011 in view of the HUMIRA Label. For the reasons provided below, Petitioner has not shown that these claims would have been obvious over the cited references.

Petitioner's obviousness challenge fails to establish that one of ordinary skill in the art would have been motivated to combine the disclosure of Gokarn Provisional[5] with the HUMIRA Label. Gokarn Provisional does not disclose adalimumab. Rather, it exemplifies an unrelated antibody (EMAB), in a *buffered* solution, at a concentration *below* that which is claimed. (*See, e.g., supra* Sections II.A.1, V.A.-B., and VI.B.1.) The HUMIRA Label concerns the commercially available 50 mg/ml *buffered* formulation of adalimumab, which uses a citrate-phosphate buffering system. (Ex. 1205, 470.)

[5] *See supra* Section V.C.

Further, as discussed above, Gokarn '011 does not qualify as prior art because Gokarn Provisional lacks adequate written description support both for the material relied upon in Petitioner's obviousness allegation and for claims 162 and 165 of Gokarn '011. (*See supra* Section V.) Consequently, the Board should deny Ground 2.

Even if Gokarn '011 were prior art (which it is not), a combination of the disclosure of Gokarn Provisional in view of the HUMIRA Label would not have rendered the challenged claims obvious. Petitioner does not establish that a skilled artisan would have been motivated to select and combine the disclosure of Gokarn Provisional and the HUMIRA Label. Neither Petitioner nor the asserted references identifies or describes any known problem with HUMIRA that would have motivated one of ordinary skill in the art to modify the highly successful adalimumab formulation of HUMIRA to eliminate the buffering system. Indeed, in articulating Ground 2, Petitioner fails to identify *any problem* that would have motivated a skilled artisan to attempt to modify HUMIRA at all. Thus, the skilled artisan would not have been motivated to choose adalimumab, particularly because it is not even mentioned in Gokarn Provisional.

Petitioner also fails to establish any reasonable expectation of success of developing a high-concentration formulation of adalimumab without a buffering system based on the disclosure of Gokarn Provisional in view of the HUMIRA

Label. The well-established unpredictability of developing liquid pharmaceutical formulations meant that one could not expect a formulation designed for one antibody to work for any other antibody (such as adalimumab). (*See, e.g.,* Ex. 1286, 5, 21.)

Due to at least these deficiencies in its arguments and evidence, Petitioner has not established that the cited prior art would have provided one of ordinary skill in the art with a reasonable expectation of successfully arriving at the claimed adalimumab pharmaceutical formulations that do not comprise a buffering system.

A. Petitioner Fails To Show That One Of Ordinary Skill In The Art Would Have Been Motivated To Remove HUMIRA's Buffering System

HUMIRA, one of the top selling drugs in the world, is used by hundreds of thousands of patients to treat rheumatoid arthritis and other inflammatory conditions. (Ex. 2042, 1.) When it was approved in 2002, HUMIRA was a breakthrough in the field of antibody therapeutics. It was the first commercialized high-concentration, liquid antibody formulation for subcutaneous administration. HUMIRA was successfully formulated as a *buffered* pharmaceutical formulation. (Ex. 1205.) Despite HUMIRA representing a significant achievement in the formulation of high-concentration monoclonal antibodies, Petitioner asserts that a skilled artisan would have been motivated to modify this formulation to remove its buffering system. (Pet. 58-59.)

But Petitioner has not identified a problem with HUMIRA that would have led one of ordinary skill in the art to remove its buffer. This is a fatal deficiency in Ground 2. *Novartis Pharm. Corp. v. Watson Labs., Inc.*, 611 F. App'x 988, 995-96 (Fed. Cir. 2015) (finding no motivation to modify a pharmaceutical formulation where the prior art did not unambiguously identify a known problem). Rather, Petitioner simply asserts that the requisite motivation comes from Gokarn Provisional.

First, Petitioner alleges that the "Gokarn Provisional expressly motivates a POSA to eliminate extraneous buffering systems from high-concentration antibody formulations." (Pet., 57.) But, as detailed above in Section VI.B.4., Petitioner fails to show that one of ordinary skill in the art would have believed that the buffers in HUMIRA were unnecessary or "extraneous" as Petitioner contends. Rather, it was known that buffers were important components required to stabilize protein formulations, and that the effect of adding or removing excipients for a particular formulation may differ vastly depending on the unique stability issues of a particular antibody. (*See supra* Section VI.B.4.)

Second, Petitioner contends that a skilled artisan reviewing the EMAB data would have immediately envisaged HUMIRA and selected adalimumab for use in a formulation without a buffering system because HUMIRA had been commercialized. (Pet., 58.) But the small genus alleged by Petitioner simply does

not exist. Rather, Gokarn Provisional is directed to the universe of *all* "antibodies" and other proteins generally. (Ex. 1204.) It also does not describe the preparation of *any* "bufferless" formulation of *any* antibody, much less at a concentration of 50-200 mg/ml. (*See, e.g., supra* Sections II.A.1, V.A.-B., & VI.B.1.) Gokarn Provisional's only data are for EMAB. (*Id.;* Ex. 1204, 4-5.) Moreover, only acetate-*buffered* and succinate-*buffered* EMAB solutions were prepared, yet those EMAB solutions could not be concentrated any higher than 46 mg/ml, at which point cloudiness appeared. (*Id.*) Gokarn Provisional acknowledges that no "bufferless" solutions were prepared, stating that "[a] more accurate estimate of the buffer capacity from EMAB alone *will have to be obtained* from bufferless high concentration EMAB solutions (*ongoing*)." (*Id.*, 13.)

The fact that HUMIRA existed as a commercial product cannot provide the requisite motivation. Obviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention. *InTouch Techs., Inc. v. VGo Commc'ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014). Even as late as 2014, the scientific literature reported the use of buffering systems, such as citrate, to produce a successful formulation. (Ex. 2028, 271 (reporting that the initial formulation of ERBITUX encountered antibody aggregation, which was addressed by "empirically optimiz[ing]" conditions and employing citrate buffer).) By failing

to establish any reason to reformulate the successful HUMIRA formulation, Petitioner's obviousness allegations are necessarily based on impermissible hindsight. *See, e.g., Leo Pharm.*, 726 F.3d at 1354 (holding that because the prior art did not recognize or disclose a stability problem, a skilled artisan would not have attempted to improve that prior art).

Notably, from HUMIRA's introduction in 2003 through the 2007 filing date of the '619 patent, only two other commercially available monoclonal antibody products were formulated for subcutaneous administration, but both were lyophilized (freeze-dried). (Ex. 1286, 2-4.) In the same time period, commercially available liquid formulations existed for fifteen other monoclonal antibody products, and all were provided with a buffering system. (*Id.*; *see also* Ex. 2055, 852.) Petitioner accordingly fails to establish that persons skilled in the art had any reason to remove buffering systems from existing antibody formulations.

Table 1. Commercially Available Antibody Formulations (2007) [6]

Antibody Product	Delivery	Form
AVASTIN	IV	Buffered Liquid
BEXXAR	IV	Buffered Liquid
CAMPATH	IV	Buffered Liquid
ERBITUX	IV	Buffered Liquid
HUMIRA	SC	Buffered Liquid
LUCENTIS	Intravitreal	Buffered Liquid
ONCOSCINT	IV	Buffered Liquid
ORTHOCLONE	IV	Buffered Liquid
PROSTASCINT	IV	Buffered Liquid
REOPRO	IV	Buffered Liquid
RITUXAN	IV	Buffered Liquid
TYSABRI	IV	Buffered Liquid
VERLUMA	IV	Buffered Liquid
ZENAPAX	IV	Buffered Liquid
ZEVALIN	IV	Buffered Liquid
RAPTIVA	SC	Lyophilized (Buffered)
XOLAIR	SC	Lyophilized (Buffered)

[6] Table adapted from Wang 2007. (Ex. 1286, 2-4 (Table 1); *see also* Ex. 2055, 852).).

The history of commercial antibody formulations subsequent to the disclosure of Gokarn Provisional confirms that skilled artisans were not, in fact, motivated to exclude buffers. Even as late as 2015, *all* commercially available aqueous monoclonal antibody formulations were provided with a buffering system. (Ex. 2051, 94-101 (Table 4.1); *see also* Ex. 2055, 852.)

At the time of the '619 patent invention, it was extremely difficult to make stable (*e.g.,* non-aggregated, non-fragmented, non-degraded, non-denatured, *etc.*), liquid formulations of antibodies, particularly at high concentrations. (*See, e.g.*, Ex. 1286, 14 ("Among all the commercial antibody products, about half are stable enough to be formulated in a liquid form.").) The same held true even several years later. (*See, e.g.,* Ex. 2028, 271 ("a considerable proportion of human monoclonal antibody candidates *fail formulation studies*"); Ex. 2020, 612; Ex. 2026, 82.) Petitioner's failure to identify a motivation to eliminate buffers from HUMIRA is dispositive, particularly in view of the demonstrated success of the HUMIRA formulation. *Leo Pharm.*, 726 F.3d at 1354; *InTouch,* 751 F.3d at 1352.

Thus, for at least these reasons, Petitioner's arguments concerning any alleged motivation fail.

B. Petitioner Fails To Demonstrate That A Person Of Ordinary Skill In The Art Would Have Had A Reasonable Expectation Of Success In Arriving At The Claimed Adalimumab Formulations

Petitioner argues that one of ordinary skill in the art would have had a reasonable expectation of success in formulating adalimumab in an aqueous formulation at 50 mg/ml without a buffering system for the same reasons addressed in Section VI.B. above. (Pet., 59.) In particular, Petitioner again alleges that a skilled artisan would have understood 50 mg/ml adalimumab to have about the same buffering capacity as 50 mg/ml EMAB, because both are IgG1 antibodies and therefore share similar amino acid sequences and tertiary structures. (*Id.*) Petitioner further alleges that HUMIRA was a "piece of prior art ready for the improvement" and that Gokarn Provisional states that high concentration antibodies in general can be formulated without an extraneous buffer. (*Id.* (citation omitted).)

But Petitioner's arguments fail for the reasons detailed in Section VI.B. Gokarn Provisional does not disclose preparing *any* formulations of *any* antibody that do not comprise a buffering system, much less at a concentration of 50-200 mg/ml. (*See, e.g., supra* Section VI.B.1.) It was also known that a formulation designed for one antibody could not reasonably be expected to be successfully applied to a different antibody, or even to an antibody with a similar sequence. (*See, e.g., supra* Section VI.B.2.) Petitioner also fails to establish that all IgG

antibodies have "highly similar" buffering capacities (*see, e.g., supra* Section VI.B.3.), does not address the consequences of removing HUMIRA's buffering system (*see, e.g., supra* Section VI.B.4.), and fails to determine adalimumab's buffer capacity (*see, e.g., supra* Section VI.B.5.).

Accordingly, one of ordinary skill in the art would not have had a reasonable expectation of successfully arriving at the formulations of adalimumab claimed in the '619 patent.

VIII. Conclusion

Petitioner does not establish that Gokarn '011 is entitled to the filing date of Gokarn Provisional and that it is prior art to the '619 patent. Further, for both Ground 1 and Ground 2, Petitioner fails to establish any motivation to combine the asserted references or any reasonable expectation of success. For these reasons, and those discussed above, Petitioner fails to establish a reasonable likelihood that any challenged claim is unpatentable. The Board should therefore deny institution.

Dated: June 11, 2017

Respectfully submitted,

/s/ *Anthony M. Insogna*

Anthony M. Insogna (Reg. No. 35,203)
Tamera M. Weisser, Ph.D. (Reg. No. 47,856)
JONES DAY
4655 Executive Drive, Suite 1500
San Diego, CA 92121-3134
Tel.: (858) 314-1200
Fax.: (844) 345-3178
Email: aminsogna@jonesday.com
Email: tweisser@jonesday.com

David M. Maiorana (Reg. No. 41,449)
JONES DAY
North Point
901 Lakeside Avenue
Cleveland, Ohio 44114-1190
Tel.: (216) 586-3939
Fax: (216) 579-0212
Email: dmaiorana@jonesday.com

William B. Raich (Reg. No. 54,386)
Michael J. Flibbert (Reg. No. 33,234)
Maureen D. Queler (Reg. No. 61,879)
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
901 New York Avenue, NW
Washington, DC 20001-4413
Tel.: (202) 408-4000
Email: william.raich@finnegan.com
Email: michael.flibbert@finnegan.com
Email: maureen.queler@finnegan.com

Attorneys for Patent Owner

CERTIFICATE OF COMPLIANCE

I, the undersigned, certify that the above Preliminary Response to Petition complies with the applicable type-volume limitations of 37 C.F.R. § 42.24(b)(1). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a), this Preliminary Response, including footnotes, contains 13,991 words, as counted by the word count function of Microsoft Word. This is less than the limit of 14,000 words as specified by 37 C.F.R. § 42.24(a)(1)(i).

Dated: June 11, 2017

/s/ *Anthony M. Insogna*

Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
4655 Executive Drive, Suite 1500
San Diego, CA 92121-3134
Tel.: (858) 314-1200
Fax.: (844) 345-3178

Attorney for Patent Owner

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that I caused to be served on the counsel for Petitioner a true and correct copy of the foregoing Patent Owner's Preliminary Response by electronic means on June 11, 2017 at the following email addresses of record:

Lead Counsel	Backup Counsel
E. Anthony Figg, Reg. No. 27,195 ROTHWELL, FIGG, ERNST & MANBECK, P.C. 607 14th Street, N.W., Suite 800 Washington, DC 20005 (202) 783-6040 efigg@rothwellfigg.com CoherusIPR619@rothwellfigg.com	Joseph A. Hynds, Reg. No. 34,627 ROTHWELL, FIGG, ERNST & MANBECK, P.C. 607 14th Street, N.W., Suite 800 Washington, DC 20005 (202) 783-6040 jhynds@rothwellfigg.com CoherusIPR619@rothwellfigg.com

Dated: June 11, 2017

/s/ *Anthony M. Insogna*
Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
4655 Executive Drive, Suite 1500
San Diego, CA 92121-3134
Tel.: (858) 314-1200

Attorney for Patent Owner