IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	Fraunhofer et al.
U.S. Patent No.:	9,085,619
Issue Date:	July 21, 2015
Appl. No.:	14/506,576
Filing Date:	October 3, 2014
Title:	ANTI-TNF ANTIBODY FORMULATIONS

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REPLACEMENT PETITION FOR *INTER PARTES* REVIEW OF UNITED STATES PATENT NO. 9,085,619 PURSUANT TO 35 U.S.C. §§ 311–319 AND 37 C.F.R. § 42

(ANTICIPATION BY GOKARN '011)

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Regulations

LIST OF EXHIBITS

Petitioner Exhibit Number	Exhibit Description
1101	U.S. Patent No. 9,085,619, Fraunhofer et al.
1102	Declaration of Klaus-Peter Radtke, Ph.D.
1103	U.S. Pub. No. 2016/0319011, Gokarn et al. ("Gokarn '011")
1104	U.S. App. 60/690,582 to Gokarn et al. filed on June 14, 2005 ("Gokarn Provisional")
1105	Physicians' Desk Reference, pp. 470-74 (58th ed. 2004) ("2003 Humira® Label").
1106	HUMIRA® Label (Jan. 2008)
1107	Adalimumab Product Approval Information, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm080610.htm (accessed January 23, 2017)
1108	Physicians' Desk Reference, pp. 925-28 (56th ed. 2002) ("GAMIMUNE® Label").
1109	SYNAGIS® Label (July 2004)
1110	AVASTIN™ Label (Feb. 2004)
1111	TYSABRI® Label (Nov. 2004)
1112	AbbVie Biotechnology Ltd., "Patent Owner's Preliminary Response," in *Coherus Biosciences Inc. v. AbbVie Biotechnology Ltd.*, IPR2016-01018, Paper No. 9 (PTAB Aug. 9, 2016)
1113	AbbVie Biotechnology Ltd., "Annex A – The Humira® Story," in Opposition Proceeding for EP1406656 (filed on Dec. 22, 2014)
1114	Christensen, "Proteins as buffers," Annals of the New York Academy of Sciences, 133:34-40 (Apr. 1966)
1115	Van Slyke, "On the Measurement of Buffer Values and on the Relationship of Buffer Value to the Dissociation Constant of the Buffer and the Concentration and Reaction of the Buffer Solution," J. Biol. Chem., 52:525–570 (1922)
1116	Gokarn et al., "Excipients for Protein Drugs," Ch. 17 in Excipient Development for Pharmaceutical, Biotechnology, and Drug Delivery Systems (Ashok Katdare & Mahesh V. Chaubal eds.,

Petitioner Exhibit Number	Exhibit Description
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1118	Nozaki & Tanford, "Examination of Titration Behavior," Methods Enzymol., 11: 715–734 (1967)
1119	Olthuis et al., "Characterization of Proteins by Means of their Buffer Capacity, Measured with an ISFET-based Coulometric Sensor–Actuator System," Biosensors & Bioelectronics, 9:743–751 (1994)
1120	Physicians' Desk Reference, pp. 558-59, 914-31, 805-07, 2026-28, 2295-97, 2524-25 (56th ed. 2002)
1121	Parslow, "Immunoglobulins & Immunoglobulin Genes," Ch. 7 in Medical Immunology, Appleton & Lange (Daniel P. Stites, Abba I. Terr, & Tristram G. Parslow eds., 9th ed. 1997)
1122	U.S. Prosecution History of App. No. 14/506,576 (U.S. Patent 9,085,619)
1123	U.S. Prosecution History of App. No. 13/774,735 (U.S. Patent 8,883,146)
1124	U.S. Prosecution History of App. No. 12/325,049 (U.S. Patent 8,420,081)
1125	U.S. Prosecution History of App. No. 61/004,992
1126	Stoner et al., "Protein–Solute Interactions Affect the Outcome of Ultrafiltration/Diafiltration Operations," J. Pharm. Sci., 93:2332–2342 (2004)
1127	"Fraunhofer Substantive Motion 3," in *Fraunhofer v. Gokarn*, Patent Interference No. 106,057 (filed on Oct. 12, 2016)
1128	Schwartz, "Diafiltration for Desalting of Buffer Exchange," BioProcess Int'l (May 2003)
1129	U.S. Pub. No. 2004/0033535, Boyle et al.
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Petitioner Exhibit Number	Exhibit Description
1132	Press Release, "Amgen and Immunomedics Announce Emphasis on Development of AMG 412 (Epratuzumab) as Combination Therapy While Closing Single Agent Trial," PRNewswire-FirstCall (Jan. 23, 2003)
1133	U.S. Pub. No. 2013/0273066, Gokarn et al. (filed as U.S. App. No. 13/797,622)
1134	U.S. Pub. No. 2012/0028877, Gokarn et al. (filed as U.S. App. No. 13/188,329)
1135	U.S. Pub. No. 2008/0311078, Gokarn et al. (filed as U.S. App. No. 11/917,188)
1136	WO 2006/138181, Gokarn et al. (filed as PCT/US2006/022599)
1137	U.S. Patent No. 6,090,382, Salfeld et al.
1138	WO 1997/029131, Salfeld et al.
1139	HUMIRA® Label (Nov. 2015)
1140	HUMIRA® Label (Oct. 2016)
1141	Vivaglobin® Label (Jan. 2006)
1142	CNJ-016 (Vaccinia Immune Globulin Intravenous) Label (Jan. 2010)
1143	GAMMAGARD LIQUID Label (April 2005)
1144	OCTAGAM® Label (Mar. 2004)
1145	Flebogamma® Label (Jan. 2004)
1146	GAMUNEX® Label (Nov. 2005)
1147	Privigen® Label (Oct. 2016)
1148	HepaGam B™ Summary Basis for Approval (Jan. 2006)
1149	Vectibix™ Label (Sept. 2006)
1150	Butler & Hamilton, "Quantitation of Specific Antibodies: Methods of Express, Standards, Solid-Phase Considerations, and Specific Applications," Ch. 9 in Immunochemistry of Solid-Phase Immunoassay, CRC Press (John E. Butler ed. 1991)
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Petitioner Exhibit Number	Exhibit Description
1152	McDonnell, "Production of Antibodies in Hybridoma and Non-hybridoma Cell Lines," Ch. 3 in Animal Cell Culture, Cell Engineering Vol. 9, 65–88 (M. Al-Rubeai ed., 2015)
1153	Akers et al., "Formulation Development of Protein Dosage Forms," Ch. 2 in Development and Manufacture of Protein Pharmaceuticals, Kluwer Academic/Plenum Publishers: New York, 47–127 (Nail et al., eds., 2002)
1154	Cleland & Langer, "Formulation and Delivery of Proteins and Peptides: Design and Development Strategies," Ch. 1 in Formulation and Delivery of Proteins and Peptides, ACS Symposium Series 567, 1–19 (1994)
1155	Hanna, The IGIV-C Study Group, "Tolerability of a New Intravenous Immunoglobulin Preparation (IGIV) in Pediatric and Adult Patients," presented at the 60th Anniversary Meeting of the American Academy of Allergy, Asthma & Immunology (Mar. 10, 2003), in J. Allergy Clinical Immunology, Vol. 111, Num. 2, part 2, a631
1156	Handbook of Pharmaceutical Excipients, Pharmaceutical Press (Raymond C. Rowe, Paul J. Sheskey, & Siân C. Owen eds., 5th ed. 2006)
1157	U.S. Pub. No. 2003/0138417, Kaisheva et al.
1158	Laursen et al., "Pain Perception after Subcutaneous Injections of Media Containing Different Buffers," Basic & Clinical Pharmacology & Toxicology, 98:218–221 (2006)
1159	Frenken et al., "Identification of the Component Part in an Epoetin Alfa Preparation that Causes Pain after Subcutaneous Injection," American J. of Kidney Diseases, 22(4): 553–556 (1993)
1160	Gelfand, "Differences Between IGIV Products: Impact on Clinical Outcome," Int'l Immunopharmacology, 6:592-99 (2006)
1161	Campath® Label (Aug. 2006)

I. INTRODUCTION

Coherus Biosciences Inc. ("Coherus") petitions for *inter partes* review ("IPR") of claims 16–19, and 24–30 of U.S. Patent No. 9,085,619 ("the '619 patent," Ex. 1101). This petition and the accompanying declaration of Klaus-Peter Radtke, Ph.D. (Ex. 1102) demonstrate that each of the elements of claims 16-19 and 24-30 (the "challenged claims"), arranged as in the claims, was anticipated by U.S. Publication No. 2016/0319011 ("Gokarn '011," Ex. 1103). Gokarn '011 properly claims priority to, and incorporates by reference, U.S. Provisional Application No. 60/690,582, filed June 14, 2005 (the "Gokarn Provisional," Ex. 1104). Gokarn '011 therefore is prior art under 35 U.S.C. § 102(e) (pre-AIA) as of its June 14, 2005 effective filing date.

The challenged claims cover formulations of the well-known monoclonal antibody, adalimumab. When the earliest claimed priority application for the '619 patent was filed on November 30, 2007, adalimumab had been commercially available as a treatment for rheumatoid arthritis for nearly five years. The commercial product, Humira®, contained 50 mg/mL adalimumab in an aqueous formulation with a citrate-phosphate buffering system and other common excipients (mannitol, sodium chloride, and polysorbate 80).

Claims 16-18 of the '619 patent purport to cover *any* aqueous pharmaceutical formulation containing 50-200mg/mL adalimumab that "does not

comprise a buffering system." Ex. 1101, 152:16-39[1] (claims 16-18). The other challenged claims do little to narrow this broad scope. Dependent claim 19 requires the presence of any "non-ionizable excipient." Dependent claims 24-30 specify pH ranges for the formulation, all of which include the pH of 5.2 that was already known to be used in Humira®.

The challenged claims are unpatentable because, years before November 2007, the Gokarn Provisional had already generically described "bufferless" high-concentration liquid formulations of therapeutic antibodies. A POSA would have readily appreciated that the most prominent member of this small genus was Humira® (50mg/mL adalimumab). The Gokarn Provisional succinctly teaches that pharmaceutical antibodies in "sufficiently high concentrations, possess adequate buffering capacity in the pH range of 4.0 to 6.0, to provide pH control for a liquid formulation." Ex. 1104, 1:5-8. It further discloses that the concentration of pharmaceutical antibody which will "obviate the need for a separate buffering agent" is about 30 mg/mL or higher. *Id.* at 2:19-23, 3:10-15, 8-9, 13. The Gokarn Provisional thus describes the limited class of liquid pharmaceutical antibodies at

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[1] All citations herein refer to the enclosed Exhibits' native page numbers, except that IPR Page numbers are used where the exhibit is a compilation or does not bear native page numbers (Exhibits 1106, 1110, 1111, 1120, 1122-1125, 1132).

concentrations of 30mg/mL or higher, and teaches their formulation without an extraneous buffer.

In the 2005-2007 timeframe, only a handful of liquid formulations containing about 30 mg/mL or higher concentrations of a pharmaceutical antibody were known. A person of ordinary skill in the art ("POSA") reading the Gokarn Provisional would have "at once envisage[d]" each member of this limited class, including 50 mg/mL adalimumab. *In re Petering*, 301 F.2d 676, 681 (CCPA 1962); *see also Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 872 (Fed. Cir. 2015). The Gokarn Provisional therefore anticipates the '619 patent claims encompassing an aqueous formulation of 50mg/mL adalimumab that does not comprise a buffering system (*i.e.*, challenged claims 16-18). The Gokarn Provisional also describes bufferless formulations comprising a non-ionizable excipient (e.g., polysorbate or polyols such as sorbitol and sucrose), and discloses a preferred pH range of 4.5 to 5.5, anticipating challenged claims 19 and 24-30.

Coherus has established, at a minimum, a reasonable likelihood that it would prevail with respect to at least one claim of the '619 patent. Indeed, all challenged claims are unpatentable as anticipated. Coherus thus respectfully requests that *inter partes* review be instituted for claims 16-19 and 24-30 of the '619 patent on the bases stated in this petition.

II. MANDATORY NOTICES

A. Real Party-in-Interest (37 C.F.R. § 42.8(b)(1))

Coherus BioSciences Inc. is the real party-in-interest.

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

The '619 patent is the subject of the following judicial or administrative matters, which may affect, or be affected by, a decision in this proceeding:

Coherus has concurrently filed three additional petitions for *inter partes* review of the '619 patent. The grounds of rejection presented in each petition are unique and non-redundant.

First, this petition details how the challenged claims are anticipated under 35 U.S.C. § 102(e) by Gokarn '011, which is prior art as of the June 14, 2005 filing date of the Gokarn Provisional.

Second, Coherus has filed a petition demonstrating that the challenged claims are anticipated by the Gokarn PCT under 35 U.S.C. §§ 102(a) and (e). The Gokarn PCT—as published on December 28, 2006 and as filed on June 8, 2006—discloses every element of the challenged claims and renders them unpatentable for anticipation or, alternatively, for obviousness in view of the 2003 Humira® Label.

Third, Coherus has filed a petition demonstrating that the challenged claims are unpatentable as obvious over the 2003 Humira® Label in view of prior art that teaches reduction of buffer capacity to make injections less painful (Fransson) and

the June 14, 2005 Gokarn '011 disclosure that high-concentration IgG antibodies can be formulated without a buffering system.

Finally, Coherus has filed a petition demonstrating that the challenged claims are unpatentable as obvious over the 2003 Humira® Label in view of Fransson and buffer-free immunoglobulin products (essentially, IgG antibodies and predominantly IgG1 antibodies), as described in the 2005 Gamimune® Label.

The grounds of rejection asserted in Coherus' four petitions rely on different and independently sufficient statutory bases and employ references with different prior art dates under 35 U.S.C. §§ 102(a), (b), and (e). Coherus respectfully requests that the Board institute IPR on all four petitions, because each petition presents independent, non-redundant arguments demonstrating that the challenged claims are unpatentable and should never have issued. *See, e.g.*, *Amendments to the Rules of Practice for Trials Before the Patent Trial and Appeal Board*, 80 Fed. Reg. 50720, 50739 (Aug. 20, 2015) (Response to Comment 12) (acknowledging concerns over partial institution "where the grounds are in different statutory classes, or when a reference may be overcome by swearing behind it").

A patent application in the same patent family is pending as U.S. Patent Application No. 15/096,043.

Additionally, pursuant to the Patent Office Trial Practice Guide, 77 Fed. Reg. 48,756, 48,760 (Aug. 14, 2012), Coherus identifies out of an abundance of

caution the following proceeding involving a patent claiming a common priority application with the '619 patent: U.S. Patent No. 8,420,081, which issued from U.S. Application Ser. No. 12/325,049 (to which the '619 patent claims priority), is the subject of U.S. Patent Interference No. 106,057 (PTAB Declared May 18, 2016).

C. Lead and Back-up Counsel (37 C.F.R. § 42.8(b)(3))

Coherus provides the following designation of counsel:

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D. Service Information (37 C.F.R. § 42.8(b)(4))

Please address all correspondence and service to counsel at the address provided in Section II.C. Coherus consents to electronic service at these same email addresses and CoherusIPR619@rothwellfigg.com.

III. PAYMENT OF FEES (37 C.F.R. § 42.103)

Coherus authorizes the Patent and Trademark Office to charge Deposit Account No. 02-2135 for the fee set forth in 37 C.F.R. § 42.15(a) for this petition and further authorizes any additional fees to be charged to this Deposit Account.

IV. REQUIREMENTS FOR IPR UNDER 37 C.F.R. § 42.104

A. Grounds for Standing under 37 C.F.R. § 42.104(a)

Coherus certifies that the '619 patent is available for IPR and that Coherus is not barred or estopped from requesting IPR of the '619 patent. Coherus is a biopharmaceutical company that is developing for U.S. regulatory approval and commercial introduction adalimumab products for the treatment of disorders such as rheumatoid arthritis and/or psoriasis.

B. Challenge under 37 C.F.R. § 42.104(b); Relief Requested

Coherus requests *inter partes* review and cancellation of Claims 16–19 and 24–30 of the '619 patent as anticipated under pre-AIA 35 U.S.C. § 102(e) by Gokarn '011 as of the June 14, 2005 filing date of the Gokarn Provisional. This Petition is accompanied by the declaration of Klaus-Peter Radtke, Ph.D. (Ex. 1102) and copies of all exhibits relied on in the Petition and Declaration.

V. BACKGROUND

A. Adalimumab Was One of the Few Therapeutic Antibodies That Had Been Described for Administration in a High-Concentration Liquid Formulation

The challenged claims of the '619 patent are directed to formulations of the anti-tumor necrosis factor alpha antibody adalimumab, and closely-related antibodies. Ex. 1101, 152:16-39 (claims 16-18); Ex. 1102 ¶¶ 57-58. Adalimumab, also known as D2E7, has been recognized for nearly two decades as an antibody with promising therapeutic activity. Ex. 1102 ¶ 27. Adalimumab is the active agent in Humira®. Ex. 1102 ¶ 28. Humira® was FDA approved for treatment of rheumatoid arthritis on December 31, 2002, and was commercially available in the United States beginning in early 2003. Ex. 1107.

From the time of its commercial launch and through November 30, 2007, Humira® was sold as a liquid formulation of adalimumab at a concentration of 50mg/mL and a pH of 5.2. Ex. 1102 ¶¶ 29-30; Ex. 1105, 470; Ex. 1106, 13. The formulation included a citrate-phosphate buffering system, sodium chloride (an ionizable excipient), mannitol and polysorbate 80 (non-ionizable excipients), and water for injection. Ex. 1102 ¶ 29; Ex. 1105, 470; Ex. 1106, 13.

As of November 2007, Humira® was one of three commercially-available pharmaceutical monoclonal antibodies in a high-concentration liquid formulation. Ex. 1102 ¶ 90. Indeed, only a small number of high concentration liquid antibody

formulations were commercialized at the time. Ex. 1102 ¶¶ 31-32, 90. This small genus included immunoglobulin products containing high concentrations of IgG antibodies derived from human plasma, such as Gamimune® and Gamunex®. *Id.* at ¶ 31, 90. Protein concentrations in such plasma-derived immunoglobulin products ranged from 50 – 180 mg/mL, and *all* of these products already were formulated without an extraneous buffering system. *Id.* at ¶¶ 42, 46-48, 52; Ex. 1108, 925. Only three monoclonal antibodies were commercialized at high concentrations, i.e., at or above 30mg/mL: Campath® (30 mg/mL), Humira® (50 mg/mL), and Synagis® (100 mg/mL). Ex. 1102 ¶ 90; Ex. 1109, 1; Ex. 1105, 470; Ex. 1161, 14. Three additional antibody products were formulated at concentrations above 15 mg/mL: Tysabri® (20 mg/mL), Avastin (25 mg/mL), and Vectibix (20 mg/mL). Ex. 1110, 2; Ex. 1111, 1; Ex. 1149, 1. Additionally, the Gokarn Provisional discloses the pharmaceutical antibody epratuzumab ("EMAB"), then in development, at a concentration of about 45 mg/mL. Ex. 1104, 8-9; Ex. 1102 ¶¶ 72-73. A POSA reading the Gokarn Provisional would have immediately envisioned each member of the small class of high concentration pharmaceutical antibodies, and would have understood the Gokarn Provisional to disclose bufferless aqueous formulations of each of them. Ex. 1102 ¶ 68, 87.

Moreover, Humira® would have been one of, if not the, most prominent example of such high-concentration monoclonal antibody liquid formulations. *Id.* at ¶¶ 91, 112. As AbbVie has previously touted to the Board, Humira® was the first monoclonal antibody to be commercialized in a high-concentration liquid formulation. Ex. 1112, 12 ("Before HUMIRA, no commercial stable, liquid, high-concentration antibody formulations had been successfully developed."). It also was widely-prescribed by the 2005-2007 timeframe. Ex. 1113, 4 ("In 2004, *HUMIRA* U.S. sales were approximately $550 Million…. *HUMIRA* accounted for … about 15% of total TNF inhibitor prescriptions in 2004. By 2006, HUMIRA had passed 20% of total TNF inhibitor U.S. prescriptions.").

B. Formulation pH and Buffer Systems

Independent claim 16 of the '619 patent covers *any* formulation of adalimumab in water without a "buffering system." Ex. 1101, 152:16-32 (claim 16). In the context of protein pharmaceuticals, buffers are compounds that meaningfully contribute to a solution's ability to resist pH change, a characteristic known as "buffer capacity." Ex. 1102 ¶ 41.

Buffer capacity refers to the ability of a solution, such as an aqueous protein formulation, to resist pH change upon the addition of acid or base. *Id*. ¶ 41; Ex. 1114, 34; Ex. 1104, 6. This ability to resist pH change comes from certain compounds in solution that have dissociable protons (e.g., weak acids and bases).

Ex. 1102 ¶ 41; Ex. 1115, 526. The dissociation constant of an acid (its "pK_a value") is a measure of the strength of an acid in solution. Ex. 1102 ¶ 41. The most efficient buffers for a given solution contain compounds that have one or more dissociable protons with a pK_a value near that of the formulation's selected pH. Ex. 1102 ¶ 41; Ex. 1115, 527 (indicating that buffers are "most efficient" when pH = pK_a); Ex. 1116, 297 ("Ninety percent of the buffering capacity exists within one pH unit of its pK_a.").

Commonly-used buffering systems for pharmaceuticals include weak organic acids (e.g., acetate, succinate, citrate), amino acids (e.g., histidine), and phosphates. *See, e.g.*, Ex. 1103 ¶ 9; Ex. 1116, 297, Table 2. Not all amino acids serve as buffers. For example, the amino acids glycine and proline often are used as stabilizers in protein formulations, but they do not act as buffers, because their pK_as are not sufficiently close to the pH at which most protein pharmaceuticals are formulated. Ex. 1102 ¶ 42 (citing Ex. 1116, 299; Ex. 1160, 595-97).

It is important that a formulation for a protein therapeutic have sufficient buffer capacity to resist pH changes during processing and storage, because proteins generally are formulated at a particular pH at which the protein is least susceptible to chemical and physical degradation. Ex. 1102 ¶¶ 38-40; Ex. 1116, 297 ("The stability of a protein drug is usually observed to be maximal in a narrow pH range."). At the same time, excessive buffer capacity is undesirable in a

formulation for therapeutic use, especially subcutaneous administration, because the formulation should rapidly adjust to the patient's physiological pH following administration. Ex. 1102 ¶ 55; Ex. 1117, 1012 (Abstract) ("[F]or subcutaneous injections at non-physiological pH, the buffer strength should be kept as low as possible to avoid pain upon injection…. [A] lower buffer strength enables more rapid normalization of the pH at the injection site.").

C. Proteins as Buffers

POSAs have known for decades that a protein, by itself, can provide buffer capacity. *See, e.g.*, Ex. 1114; Ex. 1115, 561. A protein's buffer capacity comes from the acidic or basic side chains of certain of its constituent amino acids that have dissociable protons. Ex. 1102 ¶ 42; Ex. 1118, 715. The 1966 paper entitled PROTEINS AS BUFFERS (Ex. 1114) taught that the amino acids that contribute most to buffering capacity are those whose pK_a is close to the pH of the formulation (provided that those amino acids are on the exterior of the protein, exposed to solution). Ex. 1114, 34, 36; Ex. 1102 ¶ 42.

POSAs understood that a protein's buffer capacity will increase with the number of such amino acids in each protein molecule and also with protein concentration. Ex. 1102 ¶¶ 43-44; *see also* Ex. 1119, 749–50 (demonstrating that a protein's buffer capacity increases with concentration and indicating that buffer capacity is proportional to the number of the protein's proton binding sites); Ex.

1118, 715; Ex. 1114, 34. Indeed, as early as 1922, it was recognized that the amount of buffer capacity contributed by a protein is dependent on the concentration of protein in the formulation. Ex. 1115, 539 ("It is evident . . . that the buffer effect . . . is proportional to the total molecular concentration of the buffer.").

Most protein therapeutics do not contain a sufficiently high concentration of protein for the protein itself to provide sufficient buffering capacity. Ex. 1102 ¶ 45. As detailed in Section V.A. above, before November 2007, the vast majority of commercially available liquid therapeutic protein formulations had a low protein concentration (e.g., less than 15 mg/ml). *Id.* at ¶¶ 31-32, 45; Ex. 1116, Appendix (IPR Pages 19-43) (list of FDA-approved protein formulations). A POSA would not have expected those proteins to provide sufficient buffer capacity to be the *sole* source of pH control for such formulations. Ex. 1102 ¶ 45; Ex. 1116, Appendix (IPR Pages 19-43). Accordingly, most commercially-available liquid therapeutic antibody formulations marketed as of November 2007 included a separate buffering system. Ex. 1102 ¶ 45.

Well before November 2007, however, commercially-available human plasma-derived immunoglobulin products were formulated at high protein concentrations and without a separate buffering system. Ex. 1102 ¶ 47. Many such immunoglobulin products are used to treat patients with immunodeficiency

by providing a complete array of functional IgG antibodies. *Id.* at ¶ 48; Ex. 1108, 925. Accordingly, the formulation must be effective for a wide variety of IgG antibodies, regardless of the antigen recognized by each antibody. Ex. 1102 ¶ 48. Other plasma-derived immunoglobulin products carry enhanced levels of antibodies to a particular antigen and are used when that type of antibody is indicated. *Id.* at ¶ 48; *see, e.g.*, Ex. 1120, 14-16 (BayTet® product: enriched in anti-tetanus antibody, to treat tetanus exposure). Notably, a series of such products, enriched in antibodies to different antigens, can all employ the same concentration, formulation pH, and excipients. Ex. 1102 ¶¶ 47-48 (citing BayHep®, BayRab®, BayRho®, and BayTet® products).

An example of one such immunoglobulin product is Gamimune®. Ex. 1108, 925. Gamimune® was marketed as an aqueous solution containing 5% protein (*i.e.*, 50 mg/mL) and maltose (a tonicity modifier), but without a buffering system. Ex. 1102 ¶¶ 49, 52; Ex. 1108, 925. About 98% of the protein in Gamimune® was IgG antibodies. Ex. 1102 ¶ 49; Ex. 1108, 925. The remaining protein was mostly serum albumin, along with trace amounts of IgA and IgM antibodies. Ex. 1102 ¶ 49; Ex. 1108, 925. "The distribution of IgG subclasses is similar to that found in normal serum," (Ex. 1108, 925), meaning that about 65% of the IgG is of the IgG1 subclass. Ex. 1121, 101; Ex. 1102 ¶ 50. The Gamimune® label reports that "the buffer capacity of Gamimune N, 5% is 16.5

mEq/L (~ 0.33mEq/g protein)," demonstrating that POSAs understood that the concentrated protein itself provides the buffering capacity of the formulation. Ex. 1102 ¶ 52; Ex. 1108, 925.

VI. THE '619 PATENT

A. Overview of the '619 Patent

The '619 patent, entitled "Anti-TNF Antibody Formulations," was filed on October 3, 2014, and claims priority through a series of continuation applications to a provisional application filed on November 30, 2007. The challenged claims are directed to aqueous pharmaceutical formulations comprising a) 50–200 mg/ml of an anti-TNF alpha antibody having certain sequence fragments of adalimumab, and b) water, "wherein the formulation does not comprise a buffering system." *See* Ex. 1101, 152:16-32 (claim 16).

The '619 specification describes methods and compositions for formulating proteins in only water. *Id.* at 3:34-37. The '619 patent focuses on removing all excipients, so that the protein is formulated in water with no other excipients or additives. *See, e.g.*, *id.,* 3:34-50, 10:57-61, 28:58-60 ("The aqueous formulation of the invention does not rely on standard excipients, e.g., a tonicity modifier, a stabilizing agent, a surfactant, an anti-oxidant…"); Ex. 1102 ¶¶ 58-59. The '619 patent notes that the omission of ionic excipients of all types (not just buffers) is particularly advantageous. *See, e.g.*, Ex. 1101, 28:62-64 ("In other embodiments

of the invention, the formulation contains water, one or more proteins, and no ionic excipients (e.g., salts, free amino acids); *id.* at 45:39-42.

The formulations are achieved using diafiltration ("DF") or ultrafiltration/diafiltration ("UF/DF"). *Id.* at 3:37-42, 9:28-46. These techniques were well-known in the art. *Id.* at 23:52-56 ("DF/UF may be performed in accordance with conventional techniques known in the art using water, e.g, WFI, as the DF/UF medium (e.g., Industrial Ultrafiltration Design and Application of Diafiltration Processes, Beaton & Klinkowski, J. Separ. Proc. Technol., 4(2) 1-10 (1983)).". DF and UF/DF employ a size exclusion filter that allows solvent and small-molecule excipients to pass through, but retains the protein. *Id.*at 9:21-50; 22:44-51. Ultrafiltration may be used to increase the concentration of the protein; diafiltration involves the addition of more solvent to the protein side of the filter to reduce the concentration of filter-permeable excipients. *Id.* at 9:21-46; 22:44-24:3; Ex. 1102 ¶ 59.

To prepare the compositions of the alleged invention, a first formulation of protein, which contains excipients, is diafiltered using water so that the concentration of excipients is greatly reduced. *Id.* at 3:37-42. In Example 1, for instance, an adalimumab formulation containing citrate-phosphate buffers, sodium chloride, and mannitol is diafiltered using a five-fold volume exchange with water to remove the excipients. *Id.* at 40:45-41:11. Theoretically, this filtration approach

could have removed no more than 96.875% of the excipients. *Id.* at 43:48–60. Had the applicants used "constant volume diafiltration," the *theoretical* reduction in excipients would have increased to 99.3%. *Id.* The specification acknowledges that it would have been impossible to remove all excipients by the techniques described in the '619 patent. *See id.* at 10:61–63 ("[T]he total elimination of small molecules cannot be achieved in an absolute sense by DF/UF processing . . . .").

While the claims and certain examples of the '619 patent focus on anti-TNF alpha antibodies (and in some cases adalimumab, specifically), the '619 specification recognizes that a wide-range of proteins (including antibodies) can be prepared in an excipient-free formulation. *See, e.g.*, Ex. 1101, 5:16-17 ("Any protein may be used in the methods and compositions of the invention."). Specifically, the '619 patent specification states that the following antibodies can be used in such formulations:

> 1D4.7 (anti-IL-12/anti-IL-23; Abbott Laboratories), 2.5 (E)mg1 (anti-IL-18; Abbott Laboratories), 13C5.5 (anti-1′-13; Abbott Laboratories), J695 (anti-IL-12; Abbott Laboratories), Afelimomab (Fab 2 anti-TNF; Abbott Laboratories), Humira (adalimumab (D2E7); Abbott Laboratories), Campath (Alemtuzumab), CEA-Scan Arcitumomab (fab fragment), Erbitux (Cetuximab), Herceptin (Trastuzumab), Myoscint (Imciromab Pentetate), ProstaScint (Capromab Pendetide), Remicade

> (Infliximab), ReoPro (Abciximab), Rituxan (Rituximab), Simulect (Basiliximab), Synagis (Palivizumab), Verluma (Nofetumomab), Xolair (Omalizumab), Zenapax (Daclizumab), Zevalin (Ibritumomab Tiuxetan), Orthoclone OKT3 (Muromonab-CD3), Panorex (Edrecolomab), and Mylotarg (Gemtuzumab ozogamicin) golimumab (Centocor), Cimzia (Certolizumab pegol), Soliris (Eculizumab), CNTO 1275 (ustekinumab), Vectibix (panitumumab), Bexxar (tositumomab and I131 tositumomab) and Avastin (bevacizumab).

Id. at 32:19-37. Thus, the '619 specification asserts that a wide-range of proteins (including antibodies) can be prepared in an excipient-free formulation; it does not indicate that adalimumab carries unique formulation requirements that differentiate it from the other proteins listed in the '619 specification. Ex. 1102 ¶ 58.

B. The Prosecution History

The '619 patent issued on July 21, 2015 from U.S. App. No. 14/506,576, which was filed on October 3, 2014 ("the '576 application"). Through a chain of continuation applications, the '619 patent claims priority to U.S. Provisional App. No. 61/004,992, which was filed on November 30, 2007—*nearly two and a half years after* the effective filing date of Gokarn '011. Applications in the Gokarn '011 chain of priority (e.g., WO/2006/138181, US2008/0311078) were included among a list of nearly 300 references submitted to the Patent Office by AbbVie,

but they were never addressed by the Examiner during prosecution. *See* Ex. 1122, 208, 212; *see also* Ex. 1101, References Cited.

AbbVie first presented the challenged claims in a preliminary amendment filed November 21, 2014 in the '576 application. Ex. 1122, 293 (application claim 41 corresponds to issued claim 16). Prior to filing that preliminary amendment, none of the applications in the priority chain of the '619 patent had included claims requiring the absence of a "buffering system," as opposed to excluding all ionizable excipients. Ex. 1123, 202–04, 271–73, 950–54, 1038–42; Ex. 1124, 4-14, 261-269, 1695-1704, 1738-1749, 1868-1888, 1946-1969; Ex. 1125, 145-154 .

C. The Challenged Claims

Coherus challenges claims 16–19 and 24–30. Independent claim 16 recites pharmaceutical formulations that do not comprise a "buffering system," but do comprise water and 50 to 200 mg/ml of an antibody having certain sequence fragments of adalimumab. The claim's "comprising" language encompasses compositions that include non-buffer excipients, whether ionic or non-ionic. Claims 17 and 18 limit the antibody more specifically to adalimumab, claim 19 requires the addition of "a non-ionizable excipient," and claims 24–30 limit the pH range.

VII. LEVEL OF SKILL IN THE ART

As of November 30, 2007, the education and experience level of a person of ordinary skill in the art who would have been asked to design a pharmaceutical antibody formulation would have had an advanced degree in biology, biochemistry, or chemistry (or related discipline). This person also would have had at least two years of experience preparing formulations of proteins suitable for therapeutic use. Ex. 1102 ¶¶ 61-62.

VIII. CLAIM CONSTRUCTION

Claims are interpreted using the broadest reasonable interpretation in light of the specification in which they appear. 37 C.F.R. § 42.100(b); *see also Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2146 (2016).

The only claim term that requires construction is the phrase "does not comprise a buffering system," which appears in independent claim 16. The broadest reasonable interpretation of this term, as understood by a POSA in light of the description in the '619 patent specification, is "contains no more than a *de minimis* amount of extrinsic buffer." Ex. 1102 ¶¶ 64-65. This definition is supported by the intrinsic evidence.

The '619 patent explains that the claimed formulations are produced by subjecting antibody compositions containing buffers and other excipients to filtration techniques that remove the excipients. Ex. 1102 ¶¶ 59-60; Ex. 1101, 40

e.g., Example 1. As the '619 patent acknowledges, the techniques it references cannot remove ***all*** the buffering system components. There will always be some amount of buffer, however small, remaining in the solution. *See id.* at 10:61–63 ("[T]he total elimination of small molecules cannot be achieved in an absolute sense by DF/UF processing . . . ."); Ex. 1102 ¶ 65 (explaining that protein-solute interactions limit the ability to remove buffer components); Ex. 1126, 2339.

Therefore, the phrase "does not comprise a buffering system" encompasses formulations that have a *de minimis* amount of buffer components, such as the small amounts of citrate and phosphate that would remain in the formulations of the '619 patent. Ex. 1102 ¶ 65.

IX. THE DISCLOSURE OF GOKARN '011, UPON WHICH THIS PETITION RELIES, IS AVAILABILE AS PRIOR ART UNDER 35 U.S.C. § 102(e)(1) AS OF JUNE 14, 2005

A § 102(e) prior art reference "'shall have the same effect,' including a patent-defeating effect, … as though it was filed on the date of the … provisional" to which it claims priority, as long as certain requirements are met. *In re Giacomini*, 612 F.3d 1380, 1383-84 (Fed. Cir. 2010) (quoting 35 U.S.C. § 119(e)); *Ex parte Cropper*, No. 2014-001403, 2016 WL 3541264, at *4 (PTAB June 24, 2016) (holding that *Giacomini* extends to published applications). In particular, the provisional application must disclose an invention claimed in the § 102(e) reference "in the manner provided by the first paragraph of section 112." 35

U.S.C. § 119(e)(1); *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) ("[T]he specification of the *provisional* must 'contain a written description of the invention and the manner and process of making and using it, in such full, clear, concise, and exact terms,' 35 U.S.C. § 112 ¶ 1, to enable an ordinarily skilled artisan to practice the invention *claimed* in the *non-provisional* application.") (emphasis in original).

Interpreting *Dynamic Drinkware*, 800 F.3d at 1378, the Board has held that a § 102(e) reference is available as prior art as of its provisional application's filing date when the provisional provides support for: (1) at least one claim of the § 102(e) reference, and (2) the subject matter on which the petitioner relies. *Cisco Systems, Inc. v. Capella Photonics, Inc.*, IPR2014-01276, Paper No. 40 at 21-22 (PTAB Feb. 17, 2016). Only one claim from the non-provisional application need be supported by the provisional. *See id.* at 22 n.9; *Benitec Biopharma Ltd. v. Cold Spring Harbor Lab.*, IPR2016-00017, Paper No. 7 at 7 (PTAB Apr. 6, 2016); *see also* 35 U.S.C. § 119(e)(1) (referring to "an invention disclosed").

When used as part of a § 102(e) reference, "a provisional application—like a regular utility application—constitutes prior art for all that it teaches." *Ex Parte Yamaguchi*, No. 2007-44 12, 88 USPQ2d 1606, 1612 (BPAI Aug. 29, 2008) (precedential); *see also Giacomini*, 612 F.3d at 1383 (affirming invalidity under § 102(e) where "another's patent discloses the same invention, which was carried

forward from an earlier U.S. provisional application or U.S. non-provisional application").

The discussion below demonstrates that the Gokarn Provisional provides support for: (1) Claims 162 and 165 of Gokarn '011; and (2) the subject matter on which Petitioner relies. Therefore, Gokarn '011 is available as prior art and entitled to a § 102(e) date of June 14, 2005, the filing date of the Gokarn Provisional.

A. The Gokarn Provisional (Ex. 1104) Satisfies the Requirements of Pre-AIA 35 U.S.C. § 112, ¶1 for at least Claims 162 and 165 of Gokarn '011.

To satisfy the written description requirement, "the four corners of the specification" must disclose to one of skill in the art that the inventor possessed the claimed subject matter as of the filing date. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). This must be evident from the specification but need not be word for word. *Id.* at 1352. In addition to adequately describing the claimed invention, "an applicant must describe the manner of making and using the invention 'in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the same . . . .'" *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1322 (Fed. Cir. 2005) (quoting 35 U.S.C. § 112, ¶1). Both of these requirements are satisfied by the Gokarn Provisional for at least claims 162 and 165 of Gokarn '011.

1. Claim 162 of Gokarn '011 is Supported by the Gokarn Provisional

The Gokarn Provisional discloses the subject matter in claim 162 of Gokarn '011. The sole claim of the Gokarn Provisional[2] is similar to claim 162, as shown by the following side-by-side comparison, with the minor differences in wording italicized:

Gokarn Provisional	Gokarn '011
Claim 1. *A method comprising preparing* a pharmaceutical protein formulation *containing*	Claim 162. A pharmaceutical protein formulation *comprising*:
an antibody,	an antibody
in an amount sufficient for maintaining pH control, and	in an amount sufficient for maintaining pH control; and
a pharmaceutically acceptable excipient;	a pharmaceutically acceptable excipient,
wherein said pharmaceutical protein formulation is buffered by said antibody.	wherein said pharmaceutical protein formulation is buffered by said antibody, *and wherein the formulation lacks a buffer, apart from the antibody.*

Ex. 1103, 37; Ex. 1104, 14.

2 The Gokarn Provisional appears to have been drafted to obtain a filing date on work that was about to be publicly presented, inasmuch as it contains only a single claim and the majority of its disclosure appears to be a PowerPoint presentation. *See* Ex. 1104, 4-14.

While the Gokarn Provisional is directed to a method of preparing formulations, and claim 162 of Gokarn '011 is directed to the formulation itself, a POSA would have understood that the Gokarn Provisional also described buffer-free antibody formulations, as discussed below. Ex. 1102 ¶ 78. The other minor difference is that claim 162 expressly states "wherein the formulation lacks a buffer, apart from the antibody."

A POSA would have understood that the Gokarn Provisional discloses formulations wherein the formulation lacks a buffer, apart from the antibody. *Id.* at ¶ 79. The title of the Gokarn Provisional is "***Bufferless*** Protein Formulation." Ex. 1104, 1:1 (Title) (emphasis added). The Gokarn Provisional further discloses a preferred embodiment in which "the pharmaceutically active compound is the buffering agent," *id* at 1:15-17, and teaches that "there will be a crossover concentration, wherein the antibody formulation ***will not require the addition of an extraneous buffer*** (like acetate) to maintain pH[.]" *Id.* at 3:6-13 (emphasis added).

Moreover, the Gokarn Provisional includes actual data measuring the buffering capacity of "EMAB" (epratuzumab) formulations without an extraneous buffer. *Id.* at 8-10; Ex. 1102 ¶ 79. 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 the Gokarn '011 application. Ex. 1102 ¶ 79.

The Gokarn Provisional also enables Gokarn '011 claim 162. As an initial matter, the Gokarn Provisional is presumed enabling for all it teaches. *In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012) ("[A] prior art printed publication cited by an examiner is presumptively enabling barring any showing to the contrary by a patent applicant or patentee."); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003) (holding presumption of enablement applies in district court proceedings as well as during prosecution).

Moreover, the Gokarn Provisional teaches a POSA how to make and use the subject matter within the scope of Gokarn '011 claim 162. For example, the Gokarn Provisional discloses diafiltration methods for exchanging the solvent system for EMAB formulations, Ex. 1104, 4-5, and demonstrates that the inventors had already made "bufferless high concentration EMAB solutions," *id.* at 13 (describing studies as "on-going"), *see also id.* at 8-9 (measuring buffer capacity of "EMAB alone").

Post-invention testing (such as that disclosed in Gokarn '011) also demonstrates that the Gokarn Provisional's diafiltration methods are useful to prepare buffer-free formulations of a variety of pharmaceutical antibodies. Ex. 1103, ¶¶ 379, 388, 392; *see In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995)

(finding post-invention testing relevant "to prove that the disclosure was in fact enabling when filed"); *see also Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987). Finally, AbbVie has admitted to the Board that, by June 2005, removing buffer from a protein solution was enabled. Ex. 1127, 4 (citing Ex. 1128; Ex. 1129) (stating that a POSA "would have readily known that routine techniques . . . such as dialysis or size exclusion chromatography[] could be used to remove the buffer from a protein solution.").

The Gokarn Provisional therefore discloses claim 162 of Gokarn '011 as required by § 119(e).

2. Claim 165 of Gokarn '011 is Supported by the Gokarn Provisional

Claim 165 of Gokarn '011 reads:

> The pharmaceutical protein formulation of claim **162,** wherein the antibody is epratuzumab.

Ex. 1103, 37. This claim is also described and enabled by the Gokarn Provisional. Ex. 1102 ¶¶ 80-81. The Gokarn Provisional demonstrates that Gokarn possessed buffer-free formulations of "AMG412 (Emab)" or "EMAB." Ex. 1104, 4-5, 8-10, 13. Both "Emab" and "AMG412" were widely known at the time to refer to epratuzumab. Ex. 1102 ¶ 72; Ex. 1130, 50; Ex. 1131, 3986, Figure 4; Ex. 1132, 1. Claim 165 is enabled by the Gokarn Provisional for the same reasons stated above

for claim 162. Therefore, the Gokarn Provisional sufficiently discloses claim 165 of Gokarn '011 as required by § 119(e).

B. Each Application in the Chain of Priority Satisfies the Requirements of Pre-AIA 35 U.S.C. § 112, ¶1 for Claims 162 and 165 of Gokarn '011.

A claim in a later-filed application is entitled to the benefit of a provisional application's filing date when all applications in the priority chain support the claim in the later-filed application under 35 U.S.C. § 112, ¶1. *See Holmer v. Harari*, 681 F.3d 1351, 1355 (Fed. Cir. 2012); *Butamax Advanced Biofuels LLC v. Gevo, Inc.*, IPR2013-00539, Paper No. 33 at 12 (PTAB Mar. 3, 2015).

There are four applications in the chain leading back from Gokarn '011 to the Gokarn Provisional: U.S. Application No. 13/797,622; U.S. Application No. 3/188,329; U.S. Application No. 11/917,188; and PCT/US2006/022599 (collectively, the "Intermediate Applications"). Gokarn '011 and each of the Intermediate Applications properly claim priority to the Gokarn Provisional, without a break in the priority chain. Ex. 1103 ¶1; Ex. 1133 ¶1; Ex. 1134 ¶1; Ex. 1135 ¶1; Ex. 1136, 1:3-5. Moreover, for the reasons below, each of these applications discloses claims 162 and 165 of Gokarn '011.

1. Each Application in the Chain of Priority Incorporates by Reference the Entirety of the Gokarn Provisional

An application may incorporate a provisional application by reference. *Trs. of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1365-66 (Fed. Cir. 2016). In

such cases the "provisional applications incorporated by reference are 'effectively part of the' specification as though [they were] 'explicitly contained therein.'" *Id.* (quoting *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000)).

Additionally, "broadly stating without further qualification that the earlier-filed applications are 'incorporated by reference,' is sufficient in view of Federal Circuit precedent to incorporate the disclosure of the provisional applications into each later-filed patent." *Acuity Brands Lighting, Inc., v. Lynk Labs, Inc.*, IPR2016-01116, Paper No. 10 at 42-43 (PTAB Dec. 6, 2016) (citations omitted); *see also Harari v. Lee*, 656 F.3d 1331, 1335 (Fed. Cir. 2011) ("[T]he entire . . . application disclosure was incorporated by the broad and unequivocal language: 'The disclosures of the two applications are hereby incorporate[d] by reference.'").

Each of the Intermediate Applications and Gokarn '011 incorporate the Gokarn Provisional by reference, using the same unequivocal language: "This application … claims full priority benefit of U.S. Provisional Application Ser. No. 60/690,582 filed 14 Jun. 2005, which is incorporated herein by reference in its entirety." Ex. 1103 ¶1; Ex. 1133 ¶1; Ex. 1134 ¶1; Ex. 1135 ¶1; Ex. 1136, 1:3-5. This language is sufficient to incorporate the entire disclosure of the Gokarn Provisional. *See, e.g.*, *Harari*, 656 F.3d at 1335.

As explained in Section IX.A. above, the Gokarn Provisional supports at least claims 162 and 165 of Gokarn '011, and its incorporation by reference into the Intermediate Applications and Gokarn '011 renders claims 162 and 165 supported by all applications in the priority chain. Additionally, the disclosure of the Gokarn Provisional is carried forward into each of Gokarn'011 and the Intermediate Applications, as described below.

2. Each Application in the Chain of Priority Independently Provides Pre-AIA 35 U.S.C. § 112, ¶1 Support for Claims 162 and 165 of Gokarn '011

Independent of their incorporation by reference of the Gokarn Provisional, Gokarn '011 and the Intermediate Applications (which include substantially the same specification as Gokarn '011) satisfy the written description and enablement requirements of 35 U.S.C. § 112, ¶1 with respect to claims 162 and 165. Ex. 1102 ¶¶ 82, 86, 92, 96, 102; Ex. 1133; Ex. 1134; Ex. 1135; Ex. 1136.

For example, the references' specifications disclose "pharmaceutically acceptable formulations comprising a pharmaceutical protein, that are buffered by the protein itself, that do not require additional buffering agents to maintain a desired pH, and in which the protein is substantially the only buffering agent." Ex. 1103 ¶11; Ex. 1133 ¶11; Ex. 1134 ¶11; Ex. 1135 ¶11; Ex. 1136, 3:17-20. They further explain that "'[s]elf-buffering' means the capacity of a substance, such a pharmaceutical protein, to resist change in pH sufficient for a given application, in

the absence of other buffers." Ex. 1103 ¶ 141. They describe various pharmaceutical excipients that may be included. *Id.* ¶ 308. With respect to claim 165, the specification specifically refers to epratuzumab. *Id.* ¶ 263.

Gokarn '011 also enables claims 162 and 165. As with the Gokarn Provisional, it is presumed enabling for all that it teaches. *In re Antor Media Corp.*, 689 F.3d at 1288; *Amgen, Inc.*, 314 F.3d at 1355. Moreover, Gokarn '011 discloses the same diafiltration methods for preparing the self-buffering antibody formulations that are disclosed in the Gokarn Provisional and the '619 patent. Ex. 1103 ¶¶ 357-59. Moreover, as explained in Section IX.A.1. above, AbbVie has previously informed the Board that such processes were enabled. Ex. 1127, 4 (citing Ex. 1128; Ex. 1129).

Therefore, each Intermediate Application independently satisfies the written description and enablement requirements for claims 162 and 165 of Gokarn '011, and there is no break in the priority chain.

C. The Gokarn Provisional and Every Application in the Gokarn '011 Priority Chain Disclose the Subject Matter on which Petitioner Relies

Petitioner's anticipation analysis appears in Section X below. As Section X makes clear, the subject matter on which Petitioner relies is disclosed in the Gokarn Provisional. That subject matter is also disclosed in Gokarn '011 and in the Intermediate Applications, both through the incorporation of the Gokarn

Provisional (*see* Section IX.B.1. *supra*) and independently (*see* Ex. 1102, ¶¶ 82, 86, 92, 96, 102, App'x B (citing Gokarn '011 specification)). In view of the foregoing, Gokarn '011 is available as prior art under 35 U.S.C. § 102(e) as of the June 14, 2005 filing date of the Gokarn Provisional.

X. THE CHALLENGED CLAIMS ARE UNPATENTABLE AS ANTICIPATED BY GOKARN '011 AS OF JUNE 14, 2005

The challenged claims are unpatentable as anticipated by Gokarn '011 as of its June 14, 2005 effective filing date.

A. The Disclosure of a Small Genus Anticipates Each Member

"A prior art reference can only anticipate a claim if it discloses all the claimed limitations 'arranged or combined in the same way as in the claim.'" *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012)).

A reference anticipates a claim if a POSA could take its teachings in combination with the POSA's own knowledge of the particular art and be in possession of the invention. *In re Legrice*, 301 F.2d 929, 939 (CCPA 1962); *Ex parte Steve Morsa*, No. 2011-007576, 2014 Pat. App. LEXIS 1496, at *11 (BPAI Feb. 25, 2014).

"Verbatim disclosure of a particular species is not required in every case for anticipation because disclosure of a small genus can be a disclosure of each species

within the genus." *Ineos*, 783 F.3d at 872. For example, in *In re Petering*, a prior art reference disclosed a generic chemical formula that encompassed "a vast number" of compounds, but also disclosed certain preferred side chains and exemplary compounds. 301 F.2d at 681. The Federal Circuit's predecessor court held that a POSA would understand the "the pattern of … specific preferences in connection with [the reference's] generic formula constitutes a description of a definite and limited class of compounds," which had about 20 members. *Id.* The POSA would "at once envisage each member of this limited class," and therefore the reference anticipated a claim to a specific compound within that class. *Id.* at 681-82.

Similarly, in *Ineos*, the Federal Circuit affirmed a finding that a reference that "discloses the genus of saturated fatty acid amides and states that good results are achieved with the narrower genus of saturated fatty acid amides having 12 to 35 carbon atoms" anticipated a claim specifying behenamide, a saturated fatty acid amide with 22 carbon atoms. 783 F.3d at 871-72. The challenged claim specified that behenamide was the "primary lubricant." *Id*. at 871. In support of its holding of anticipation, the Federal Circuit cited an expert declaration that explained that behenamide is a common fatty acid amide lubricating agent used in the relevant industry. *Id.* at 872.

Although anticipation by a small genus often arises in the context of chemical disclosures, it is not limited to that field. Instead, anticipation may be found in any instance where a POSA would recognize that a reference discloses a small genus and could "at once envisage" each member of the class. *See, e.g.*, *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1380 (Fed. Cir. 2001) (remanding for determination of whether "there were so few suitable classes of premedicants that Kris's general suggestion to premedicate would have been understood by one of skill in the art as a suggestion to premedicate with steroids, antihistamines, and H[2]-receptor agonists, as in claims 6 and 9 of the '537 patent").

What the reference discloses is viewed from the perspective of a POSA, and the Board may consider extrinsic evidence to determine that meaning. *See, e.g.*, *In re Baxter Travenol Labs*, 952 F.2d 388, 390 (Fed. Cir. 1991) (permitting extrinsic evidence to explain that a POSA would have understood the phrase "[Baxter] Travenol's commercial, two blood bag container" referred to a bag plasticized with DEHP); *Helifix Ltd. v. Blok-Lok, Ltd.*, 208 F.3d 1339, 1347 (Fed. Cir. 2000) (observing that a prior art brochure that "does not expressly disclose in words" every claim element "might nevertheless be anticipating if a person of ordinary skill in the art would understand the brochure as disclosing [every element] and if

such a person could have combined the brochure's description of the invention with his own knowledge to make the claimed invention").

B. The Challenged Claims are Anticipated

Claim 16 of the '619 patent (the only independent claim challenged) recites "[a]n aqueous pharmaceutical formulation comprising" four elements:

[1] "an anti-tumor necrosis factor alpha antibody comprising [certain amino acid sequences of **adalimumab**]";

[2] "wherein the concentration of the antibody is **50 to 200 mg/ml**"; and

[3] "**water**";

[4] "wherein the formulation **does not comprise a buffering system**."

Ex. 1101, claim 16; Ex. 1102 ¶ 83; *Compare* Ex. 1101, SEQ ID Nos 3-8, *with* Ex. 1137, SEQ ID Nos 3-8. The claim therefore covers *any* aqueous formulation containing 50-200 mg/mL adalimumab that does not include a buffer.

Claim 17 depends from claim 16 and requires certain additional amino acid sequences, which are also present in adalimumab. Ex. 1101, claim 17; Ex. 1102 ¶ 104; *Compare* Ex. 1101, SEQ ID Nos 1-2, *with* Ex. 1137, SEQ ID Nos 1-2. Claim 18 depends from claim 17 and requires "wherein the antibody is adalimumab." Ex. 1101, claim 18; Ex. 1102 ¶ 104. Thus, the antibody required by each of claims 16-18 is satisfied by a disclosure of adalimumab. *See* 35 U.S.C. § 112, ¶4 (requiring that a dependent claim further limit the claim from which it depends).

Because claim 18 depends from and incorporates all of the limitations of claims 16 and 17, a reference that anticipates claim 18 will also necessarily anticipate claims 16 and 17. *See Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1344 (Fed. Cir. 2009). Claim 18 is therefore representative of claims 16-18.

1. The Gokarn Provisional and Gokarn '011 disclose every limitation of claim 18, arranged as in the claim.

A POSA reading the Gokarn Provisional would "at once envisage" 50mg/mL adalimumab in an aqueous, buffer-free formulation and would be in possession of the invention of claim 18. *In re Petering*, 301 F.2d at 681; *In re Legrice*, 301 F.2d at 939; Ex. 1102 ¶¶ 87-91, 93. As detailed below, the Gokarn Provisional discloses a formulation that meets every element of claim 18, arranged as in the claim. Ex. 1102 ¶¶ 84-105. That disclosure is reiterated by, and incorporated by reference in, Gokarn '011. Ex. 1102 ¶¶ 86, 92, 96, 100, 102. Gokarn '011 therefore anticipates claims 16-18 of the '619 patent under § 102(e) as of the June 14, 2005 filing date of the Gokarn Provisional.

a. The Gokarn Provisional and Gokarn '011 disclose the preamble.

As an initial matter, Coherus does not concede that the preamble is limiting. Nonetheless, the Gokarn Provisional discloses aqueous pharmaceutical formulations. Ex. 1102 ¶ 85. The Gokarn Provisional states that "the invention relates to *liquid formulations* and methods of formulating protein *pharmaceuticals*

wherein the active protein compound in the pharmaceutical formulation is the primary source of the pH control." Ex. 1104, 1:9-13 (emphasis added). A person of ordinary skill in the art would have understood that a "liquid formulation" of a "protein pharmaceutical" is an aqueous formulation. Ex. 1102 ¶ 85; *see* Section X.B.1.c *infra* (discussing the claim element "water"). Gokarn '011 incorporates these same disclosures of the preamble, and also reiterates them in its own words, as noted by Dr. Radtke. *Id.* ¶ 86.

b. The Gokarn Provisional and Gokarn '011 disclose adalimumab at a concentration of 50 mg/mL.

The Gokarn Provisional discloses adalimumab at a concentration of 50 mg/mL through its disclosure of the small genus of high concentration, liquid pharmaceutical antibody formulations. Ex. 1102 ¶¶ 87, 91. A POSA would have immediately envisioned each member of this small class, including Humira®'s 50 mg/mL adalimumab. *Id.* at ¶¶ 87, 89-91.

The Gokarn Provisional discloses that "*antibodies* at *sufficiently high concentrations*, possess adequate buffering capacity in the pH range of 4.0 to 6.0, to provide pH control for *a liquid formulation*." Ex. 1104, 1:5-8 (emphasis added). The Gokarn Provisional is also expressly directed to *pharmaceutical* antibodies. *Id.* at 1:9-13, 1:31-2:4; Ex. 1102 ¶ 87-88. The sole claim of the Gokarn Provisional points to this same small genus, claiming a method for "preparing a *pharmaceutical* protein formulation containing an *antibody, in an amount*

sufficient for maintaining pH control…" Ex. 1104, 14 (emphasis added); Ex. 1102 ¶ 89. The Gokarn Provisional provides data showing that the antibody epratuzumab ("EMAB") "exhibits significant buffer capacity at higher Ab concentrations (> 30 mg/mL) in pH 4.5 to 5.5 range." Ex. 1104, 13; Ex. 1102 ¶ 75. The Gokarn Provisional explains that other antibodies will have similar buffer capacity at the same concentrations. Ex. 1104, 2:15-3:15; Ex. 1102 ¶ 75.

Thus, a person of ordinary skill in the art would have understood that the Gokarn Provisional discloses the specific genus of liquid pharmaceutical antibodies formulated in high concentrations (*i.e.*, around 30 mg/mL or higher). Ex. 1102 ¶¶ 87, 89. *See, e.g.*, *In re Petering*, 301 F.2d at 681 (identifying the small genus disclosed to a POSA based on the "pattern of … specific preferences" disclosed by the reference); *Ineos*, 783 F.3d at 872 (identifying a small disclosed genus based on preferred groups disclosed by the reference). The Gokarn Provisional teaches that antibodies in this genus can be formulated without requiring "the addition of an extraneous buffer." Ex. 1104, 3:10-15; Ex. 1102 ¶ 91.

The genus of liquid pharmaceutical antibodies known to be formulated at concentrations of at least about 30 mg/mL was extremely limited in November 2007. Ex. 1102 ¶¶ 31, 45, 90. This small genus included epratuzumab (EMAB) at about 45 mg/mL, as disclosed in the Gokarn Provisional; a number of human plasma-derived immunoglobulin products such as Gamimune®—all of which were

already formulated without a buffering system; ATGAM® (horse-derived gamma globulin at 50 mg/mL without a buffering system); Campath® (alemtuzumab at 30 mg/mL); Humira® (adalimumab at 50 mg/mL); and Synagis® (palivizumab at 100 mg/mL). *Id.* at ¶¶ 31, 90. Even including antibodies formulated at 20 mg/mL or higher would add only three members to the class (Avastin®, Tysabri®, and Vectibix®). *Id.* at ¶¶ 32, 90. A POSA would have known of these products, and therefore a POSA reading the Gokarn Provisional would have "at once envisage[d] each member of this limited class." *In re Petering*, 301 F.2d at 681; Ex. 1102 ¶ 87.

Moreover, Humira® (adalimumab at 50 mg/mL) was the most prominent example of a liquid pharmaceutical antibody formulated at 30 mg/mL or higher. Ex. 1102 ¶¶ 46, 91. Humira® was the first high-concentration liquid antibody formulation to be commercialized, and it was widely prescribed. Ex. 1113, 4; Ex. 1112, 12; Ex. 1102 ¶ 91. Upon reading the Gokarn Provisional, a POSA would have immediately envisioned adalimumab at 50 mg/mL (as in Humira®) as providing sufficient buffering capacity in the 4.5 to 5.5 range for a "bufferless" formulation. Ex. 1102 ¶¶ 87-91.

This disclosure of 50 mg/mL adalimumab anticipates the claimed concentration range of 50-250 mg/mL. *Ineos*, 783 F.3d at 869 (holding that a claimed range "is anticipated by a prior art reference if the reference discloses a point within the range").

A person of ordinary skill in the art also would have understood from the examples in the Gokarn Provisional that an antibody concentration of approximately 50 mg/ml or greater would be a "sufficiently high concentration" to provide buffering capacity in the 5.0 to 5.5 pH range. Ex. 1102 ¶¶ 94-95; Ex. 1104, 9 (disclosing that at a pH of 5.0 to 5.5, approximately 50 mg/mL of EMAB has as much buffering capacity as a traditional acetate buffering system). This concentration range of 50 mg/mL or greater encompass the range of 50 – 200 mg/mL required by the challenged claims. A POSA would not expect that the 200 mg/mL ceiling on the concentration range claimed in the '619 patent is critical to the operability of the alleged invention. Ex. 1102 ¶ 97. Absent a showing by the patentee that the narrower range is somehow critical to the operability of the invention, the broader range anticipates. *See Ineos*, 783 F.3d. at 870-71; *ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed. Cir. 2012).

Gokarn '011 incorporates these same disclosures of adalimumab at 50 mg/mL, and also reiterates them in its own words, as noted by Dr. Radtke. Ex. 1102 ¶¶ 92-96.

c. The Gokarn Provisional and Gokarn '011 disclose that the formulation comprises water.

The Gokarn Provisional is directed to "liquid" antibody formulations, which a POSA would have understood to refer to aqueous formulations (i.e., formulations

with water as a solvent). Ex. 1104, 1:5-12; Ex. 1102 ¶¶ 85, 98. This is so because pharmaceutical proteins are routinely formulated in aqueous solutions (i.e., a solution in which water is present). Ex. 1102 ¶¶ 85, 98-99. Proteins are functional in water, and water is by far the solvent of choice for pharmaceutical protein formulations because it is non-toxic. *Id.* ¶ 85.

It is common in the art to refer to aqueous formulations simply as "liquid" formulations, as distinguished from lyophilized formulations. *Id.*; *see, e.g.*, Ex. 1116, Appendix (IPR Pages 19-43). In a lyophilized formulation, the protein is supplied as a dry solid, and then reconstituted near the time of administration with water for injection ("WFI") or an aqueous solution (e.g., salt water, water with 0.9% benzyl alcohol, or the like). Ex. 1102 ¶ 85; *see, e.g.*, Ex. 1116, Appendix (IPR Pages 19-43) (listing protein therapeutics). Water is always used as the primary solvent in a pharmaceutical protein formulation, and its presence often literally goes without saying. Ex. 1102 ¶¶ 85, 99.

For these reasons, water is the solvent in each of the known formulations within the small genus of liquid high concentration pharmaceutical formulations disclosed by the Gokarn Provisional. *Id.* at ¶ 99. Thus, the Gokarn Provisional discloses that the formulation comprises water.

Gokarn '011 incorporates these same disclosures, and also reiterates them in its own words, as noted by Dr. Radtke. Ex. 1102 ¶¶ 86, 100.

d. The Gokarn Provisional and Gokarn '011 disclose that the formulation "does not comprise a buffering system."

As explained in Section VIII (claim construction), the '619 patent makes clear that a formulation "does not comprise a buffering system" as long as the formulation derives all but a *de minimis* amount of its buffer capacity from the antibody itself; the elimination of all extraneous buffering compounds is not required. *See also* Ex. 1102 ¶¶ 64-65.

The Gokarn Provisional's entire disclosure is directed to formulations that do not comprise a buffer apart from the protein. Ex. 1102 ¶¶ 68, 101; *see also* Section IX.A.1 *supra.* The title of the application is "Bufferless Protein Formulations." Ex. 1104, 1:1. The preferred embodiment is one in which "the pharmaceutically active compound is *the* buffering agent." *Id.* at 1:15-17 (emphasis added). As an example, the Gokarn Provisional discloses formulations where "EMAB alone has significant buffering capacity." *Id.* at 8. Thus, a person of ordinary skill in the art would have understood the Gokarn Provisional to disclose formulations that do not comprise a buffering system. Ex. 1102 ¶ 101.

Gokarn '011 incorporates these same disclosures, and also reiterates them in its own words, as noted by Dr. Radtke. Ex. 1102 ¶ 102.

2. The Gokarn Provisional and Gokarn '011 disclose that the self-buffering formulation includes a non-ionizable excipient, as claimed in claim 19.

Claim 19 depends from claim 18 and requires that "the formulation further comprises a non-ionizable excipient." Ex. 1101, 152:40-41. The '619 patent defines the term "non-ionizable excipient" as "an agent having no net charge." *Id.* at 9:63-66. The '619 patent explains that "[e]xamples of non-ionic excipients include, but are not limited to, sugars (e.g., sucrose), sugar alcohols, (e.g., mannitol), and non-ionic surfactants (e.g., polysorbate 80)." *Id.* at 10:1-3.

The bufferless formulations of the Gokarn Provisional can comprise "other desired ingredients." Ex. 1104, 1:26-27. Among the additional ingredients expressly disclosed by the Gokarn Provisional are "surfactants (e.g. polysorbate)" and "polyols (e.g. trehalose, sorbitol and sucrose)." *Id.* at 1:26-30. Polysorbate and the polyols trehalose, sorbitol and sucrose are non-ionizable excipients. Ex. 1102 ¶ 107; Ex. 1101, 10:1-3. Accordingly, the Gokarn Provisional discloses a buffer-free formulation comprising 50 mg/mL adalimumab, water, and a non-ionic excipient, anticipating claim 19 of the '619 patent. Ex. 1102 ¶¶ 107, 109.

Gokarn '011 incorporates these same disclosures of a non-ionic excipient, and also reiterates them in its own words, as noted by Dr. Radtke. Ex. 1102 ¶ 108.

3. The Gokarn Provisional and Gokarn '011 disclose the pH ranges in claims 24-30.

Claims 24 and 27 depend from claims 16 and 18, respectively, and require that "the pH of the formulation is from 4 to 8." Claims 25 and 28 depend from claims 16 and 18, respectively, and require that "the pH of the formulation is from 4 to 6." Claims 26 and 29 depend from claims 16 and 18, respectively, and require that "the pH of the formulation is from 5 to 6." Claim 30 depends from claim 18 and requires that the pH is 5.2. Ex. 1101, 152:52-65 (claims 24-30).

As explained above in Section X.B.1.b, a POSA reading the Gokarn Provisional would have immediately envisioned Humira® as the most prominent example of the small class of high-concentration, liquid pharmaceutical antibodies disclosed by the Gokarn Provisional. Ex. 1102 ¶¶ 89-91, 93. As a POSA would have known, Humira® is formulated at a pH of 5.2. *Id.* ¶ 112; Ex. 1105, 470. The disclosure of pH of 5.2 is identical to the pH claimed in claim 30, and anticipates the broader pH ranges of claims 24-29. *See Ineos*, 783 F.3d at 869 (a range is anticipated by the disclosure of a point within the range).

Additionally, the Gokarn Provisional teaches a preferred pH for the self-buffering protein formulation of 4.5 to 5.5, based on its specific examples. Ex. 1102 ¶¶ 89, 112; Ex. 1104, 8-9. This narrow range anticipates very similar pHs claimed in claims 24-30. *See Ineos*, 783 F.3d at 870-71 (holding that absent a showing of criticality, the prior art's disclosure of a range that encompasses the

claimed range is anticipatory). There is no evidence of criticality here, especially because the '619 patent itself claims any formulation within the broad pH range of 4 to 8. Ex. 1102 ¶ 114; Ex. 1101, claims 24 and 27.

Gokarn '011 incorporates these same disclosures of the formulation pH, and also reiterates them in its own words, as noted by Dr. Radtke. Ex. 1102 ¶ 113.

4. The Gokarn Provisional and Gokarn '011 Enable the Claimed Bufferless Formulations of Adalimumab

As described in Section IX.A.1 above, the Gokarn Provisional enables the formulations of adalimumab and water that "do not comprise a buffering system." The Gokarn Provisional discloses diafiltration methods for exchanging the solvent system for antibody formulations. Ex. 1102 ¶ 81; Ex. 1104, 4-5. The '619 patent itself confirms that the basic diafiltration methods disclosed in the Gokarn Provisional are effective in preparing formulations of 50-200 mg/mL adalimumab that "do not comprise a buffering system," including at pH 5.2. Ex. 1101, 43:1-44:57 (Table 2 reports pH 5.22 and concentration 175 mg/mL after UF/DF processing); *see In re Brana*, 51 F.3d at 1567 n.19 (holding later testing can confirm enablement as of the critical date). Moreover, AbbVie has admitted to the Board that, by June 2005, removing buffer from a protein solution was enabled. Ex. 1127, 4 (citing Ex. 1128; Ex. 1129).

5. Claim Chart Summarizing Anticipation by Gokarn '011 as of the June 14, 2005 Filing Date of the Gokarn Provisional

The following claim chart summarizes representative disclosures showing how the Gokarn Provisional anticipates the challenged claims.

'619 Patent Claim	Gokarn Provisional (Filed June 14, 2005)
Claim 16. An aqueous pharmaceutical formulation comprising:	*The preamble is non-limiting.* "[T]he invention relates to *liquid formulations* and methods of formulating protein *pharmaceuticals* wherein the active protein compound in the *pharmaceutical formulation* is the primary source of the pH control." Ex. 1104, 1:9-13; Ex. 1102 ¶ 85.
(a) an anti-tumor necrosis factor alpha antibody comprising a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO:5; and a CDR1 domain comprising the amino acid sequence of SEQ ID NO:7, and a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO:6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO:8,	"Inventors have demonstrated that *antibodies at sufficiently high concentrations*, possess adequate buffering capacity in the pH range of 4.0 to 6.0, to provide pH control for a *liquid formulation*." Ex. 1104, 1:5-8; *see also id.* at 14, claim 1. "'*Pharmaceutical protein* formulation' refers to a protein preparation containing at least one active protein ingredient which is considered to be sufficiently effective in the treatment of a condition (e.g., disease, disorder, undesirable physiological condition.")." Ex. 1104, 1:31-2:1. A person of ordinary skill in the art would have understood that the Gokarn Provisional's disclosure of high concentration liquid pharmaceutical

'619 Patent Claim	**Gokarn Provisional (Filed June 14, 2005)**
	antibody included 50 mg/mL adalimumab as one of a small handful of such formulations. Ex. 1102 ¶¶ 87, 89-91, 95. Adalimumab comprises these sequences. *Compare* Ex. 1101 SEQ IDs, *with* Ex. 1137, SEQ IDs. This is further demonstrated by claim 18 of the '619 patent, which is dependent on claim 16 and recites adalimumab. *See* 35 U.S.C. § 112, ¶ 4.
wherein the concentration of the antibody is 50 to 200 mg/ml; and	A person of ordinary skill in the art would have understood that the Gokarn Provisional's disclosure of high concentration liquid pharmaceutical antibodies included 50 mg/mL adalimumab as one of a small handful of such formulations. Ex. 1102 ¶¶ 87, 89-91, 95. "At ~ 50 mg/mL EMAB, its buffer capacity is equivalent to 10 mM acetate." Ex. 1104, 9. "The crossover concentration[ ] of EMAB … [is] ~ 50 mg/mL in the pH 5.0-5.5 range." *Id.* at 13.
(b) water;	"[T]he invention relates to *liquid formulations* and methods of formulating *protein pharmaceuticals…*" Ex. 1104, 1:9-11. A person of ordinary skill in the art would have understood that protein liquid formulations refer to formulations in which water is a solvent. Ex. 1102 ¶¶ 85, 98-99.

'619 Patent Claim	**Gokarn Provisional (Filed June 14, 2005)**
wherein the formulation does not comprise a buffering system.	The title of the application is "Bufferless Protein Formulations." Ex. 1104, 1:1. "In the preferred embodiment of the invention, the pharmaceutically active compound is the buffering agent." *Id.* at 1:15-17. "EMAB alone has significant buffering capacity." *Id.* at 8.
Claim 17. The formulation of claim 16, wherein the antibody comprises a LCVR comprising the amino acid sequence set forth in SEQ ID NO:1, and a HCVR comprising the amino acid sequence set forth in SEQ ID NO:2.	"Inventors have demonstrated that antibodies at sufficiently high concentrations, possess adequate buffering capacity in the pH range of 4.0 to 6.0, to provide pH control for a liquid formulation." *Id*. at 1:5-8. "'*Pharmaceutical protein* formulation' refers to a protein preparation containing at least one active protein ingredient which is considered to be sufficiently effective in the treatment of a condition (e.g., disease, disorder, undesirable physiological condition.")." Ex. 1104, 1:31-2:1. A person of ordinary skill in the art would have understood that the Gokarn Provisional's disclosure of high concentration liquid pharmaceutical antibody included 50 mg/mL adalimumab as one of a small handful of such formulations. Ex. 1102 ¶ 87, 89-91, 95. Adalimumab comprises these sequences. *Compare* Ex. 1101 SEQ IDs, *with* Ex. 1137, SEQ IDs. This is further

'619 Patent Claim	**Gokarn Provisional (Filed June 14, 2005)**
	demonstrated by claim 18 of the '619 patent, which is dependent on claim 16 and recites adalimumab. *See* 35 U.S.C. § 112, ¶4.
Claim 18. The formulation of claim 17, wherein the antibody is adalimumab.	*See above for claim 17.*
Claim 19. The formulation of claim 16, wherein the formulation further comprises a non-ionizable excipient.	"Such desired ingredients include, without limitation, surfactants (e.g. polysorbate), polyols (e.g. trehalose, sorbitol and sucrose)…." *Id.*at 1:27-30.
Claim 24. The formulation of claim 16, wherein the pH of the formulation is from 4 to 8.	A POSA would have immediately envisioned Humira® (adalimumab at 50 mg/mL), which is formulated at pH 5.2. Ex. 1102 ¶¶ 91, 112. "Inventors have demonstrated that antibodies at sufficiently high concentrations, possess adequate buffering capacity in the pH range of 4.0 to 6.0, to provide pH control for a liquid formulation." *Id*. at 1:5-8.
Claim 25. The formulation of claim 16, wherein the pH of the formulation is from 4 to 6.	*See above for claim 24.*
Claim 26. The formulation of claim 16, wherein the pH of the formulation is from 5 to 6.	*See above for claim 24-25.* Further, "EMAB exhibits significant buffer capacity at higher Ab concentrations (> 30 mg/mL) in pH 4.5 to 5.5 range." Ex. 1104, 13.

'619 Patent Claim	**Gokarn Provisional (Filed June 14, 2005)**
Claim 27. The formulation of claim 18, wherein the pH of the formulation is from 4 to 8.	A POSA would have immediately envisioned Humira® (adalimumab at 50 mg/mL), which is formulated at pH 5.2. Ex. 1102 ¶¶ 91, 112. "Inventors have demonstrated that antibodies at sufficiently high concentrations, possess adequate buffering capacity in the pH range of 4.0 to 6.0, to provide pH control for a liquid formulation." Ex. 1104, 1:5-8.
Claim 28. The formulation of claim 18, wherein the pH of the formulation is from 4 to 6.	*See above for claim 27.*
Claim 29. The formulation of claim 18, wherein the pH of the formulation is from 5 to 6.	*See above for claims 27-28.* Further, "EMAB exhibits significant buffer capacity at higher Ab concentrations (> 30 mg/mL) in pH 4.5 to 5.5 range." Ex. 1104, 13.
Claim 30. The formulation of claim 18, wherein the pH of the formulation is 5.2.	*See above for claims 27-29.*

XI. CONCLUSION

For all the reasons stated above, Petitioner respectfully requests that the Board institute *inter partes* review of claims 16-19 and 24-30 of the '619 patent on the grounds set forth in this petition.

Respectfully submitted,

Dated: April 10, 2017

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4) and 42.205(b), the undersigned certifies that on April 10, 2017, a complete and entire copy of the foregoing Coherus BioSciences Inc.'s Replacement Petition for *Inter Partes* Review of U.S. Patent No. 9,085,619, along with replacement exhibits 1102, 1105 and 1108, were served on counsel for Patent Owner via email (by consent), as follows:

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CERTIFICATE OF COMPLIANCE

In accordance with 37 CFR 42.24, as amended, the undersigned certifies that this Petition complies with the applicable type-volume limitations of 37 CFR 42.24(a)(i). Exclusive of the portions exempted by 37 CFR 42.24(a), this Petition contains 10,528 words as counted by the word processing program used for its preparation (Microsoft Word 2007).

Dated: April 10, 2017

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