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

Mail Stop Patent Board
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

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 PCT; OBVIOUSNESS OVER GOKARN PCT IN VIEW OF THE 2003 HUMIRA® LABEL)

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Regulations

LIST OF EXHIBITS

Petitioner Exhibit No.	Document
1001	U.S. Patent No. 9,085,619, Fraunhofer et al.
1002	Declaration of Klaus-Peter Radtke, Ph.D.
1003	WO 2006/138181, Gokarn et al. (Published Dec. 28, 2006)
1004	U.S. App. 60/690,582 to Gokarn et al., filed on June 14, 2005 ("Gokarn Provisional")
1005	Physician's Desk Reference, pp. 470-74 (58th ed. 2004) ("2003 HUMIRA® Label").
1006	HUMIRA® Label (Jan. 2008)
1007	Parslow, "Immunoglobulins & Immunoglobulin Genes," Ch. 7 in Medical Immunology, Appleton & Lange (Daniel P. Stites, Abba I. Terr, & Tristram G. Parslow eds., 9th ed.1997)
1008	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)
1009	Jefferis et al., "Recognition Sites on Human IgG for Fcγ Receptors: The Role of Glycosylation," Immunology Letters, 44: 111-117 (1995)
1010	Christensen, "Proteins as buffers," Annals of the New York Academy of Sciences, 133:34-40 (Apr. 1966)
1011	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)
1012	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., 2006)
1013	Fransson & Espander-Jansson, "Local Tolerance of Subcutaneous Injections," J. Pharm. Pharmacol., 48:1012-1015 (1996)
1014	Nozaki & Tanford, "Examination of Titration Behavior," Methods Enzymol., 11:715–734 (1967)
1015	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)

Petitioner Exhibit No.	Document
1016	Physicians' Desk Reference, pp. 925-28 (56th ed. 2002) ("GAMIMUNE® Label").
1017	U.S. Prosecution History of App. No.14/506,576 (U.S. Patent 9,085,619)
1018	U.S. Prosecution History of App. No. 13/774,735 (U.S. Patent 8,883,146)
1019	U.S. Prosecution History of App. No. 12/325,049 (U.S. Patent 8,420,081)
1020	U.S. Prosecution History of App. No. 61/004,992
1021	Stoner et al., "Protein–Solute Interactions Affect the Outcome of Ultrafiltration/Diafiltration Operations," J. Pharm. Sci., 93:2332–2342 (2004)
1022	PCT/US2006/022599, Gokarn et al. (filed on June 8, 2006)
1023	U.S. Patent No. 6,090,382, Salfeld et al.
1024	"Fraunhofer Substantive Motion 3," in *Fraunhofer v. Gokarn*, Patent Interference No. 106,057 (filed on Oct. 12, 2016)
1025	Schwartz, "Diafiltration for Desalting of Buffer Exchange," BioProcess Int'l (May 2003)
1026	U.S. Pub. No. 2004/0033535, Boyle et al.
1027	Thomson Reuters, "A Bioworld Special Report: Biosimilars: U.S. Market Opportunities and Critical Strategies 2016" (2016)
1028	WO 1997/029131, Salfeld et al. (Published Aug. 14, 1997)
1029	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)
1030	Adalimumab Product Approval Information, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm080610.htm (accessed January 23, 2017)
1031	HUMIRA® Label (Nov. 2015)
1032	HUMIRA® Label (Oct. 2016)
1033	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.,

Petitioner Exhibit No.	Document
	eds., 2002)
1034	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)
1035	Handbook of Pharmaceutical Excipients, Pharmaceutical Press (Raymond C. Rowe, Paul J. Sheskey, & Siân C. Owen eds., 5th ed. 2006)
1036	U.S. Pub. No. 2003/0138417, Kaisheva et al.
1037	Laursen et al., "Pain Perception after Subcutaneous Injections of Media Containing Different Buffers," Basic & Clinical Pharmacology & Toxicology, 98:218–221 (2006)
1038	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)
1039	AbbVie Biotechnology Ltd., "Annex A – The Humira® Story," in Opposition Proceeding for EP1406656 (filed on Dec. 22, 2014)

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. 1001). This petition and the accompanying declaration of Klaus-Peter Radtke, Ph.D. (Ex 1002) demonstrate that each of the elements of claims 16-19 and 24-30 (the "challenged claims"), arranged as in the claims, is anticipated by PCT/US2006/022599 (the "Gokarn PCT," Ex. 1003), and also is obvious over the Gokarn PCT in view of the 2003 Humira® Label (Ex. 1005).

The challenged claims cover formulations of the well-known monoclonal antibody, adalimumab. The '619 patent claims priority to November 30, 2007. In November 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 at pH 5.2 with a phosphate/citrate buffering system and other common excipients (mannitol, sodium chloride, and polysorbate 80). Ex. 1005, 470.[1]

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

[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 1006, 1017-1020).

comprise a buffering system." Ex. 1001, 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®.

There is nothing novel about the challenged claims. *Eighteen months* before the earliest claimed priority date of the '619 patent, Gokarn filed a PCT application entitled "Self-Buffering Protein Formulations" (Ex. 1003). The Gokarn PCT, filed June 8, 2006, teaches that proteins and antibodies can be formulated at high concentration (e.g., 50 mg/mL) without a separate buffering system, and will still maintain a stable pH during formulation and storage. The Gokarn PCT expressly teaches that "HUMIRA (adalimumab)" is a suitable protein for such self-buffering formulations. The Gokarn PCT also discloses the concentration, pH, and "non-ionizable excipient" required by certain of the challenged claims. Not only was the Gokarn PCT filed well before November 30, 2007, it *published* on December 28, 2006 – nearly *eleven months* before the earliest priority document for the '619 patent was even filed.

The alleged invention of buffer-free adalimumab formulations in the challenged claims was unquestionably within the prior art before the earliest claimed priority document for the '619 patent was filed. As explained in detail

below, the Gokarn PCT anticipates the challenged claims, because it discloses every limitation, arranged as in the claims.

The challenged claims also are obvious over the Gokarn PCT in view of the 2003 Humira® Label. The Humira® Label teaches the use of exactly 50 mg/mL adalimumab at a pH of 5.2. A POSA would have expected success in using this specific concentration and pH (which were already FDA-approved and successfully commercialized) in the self-buffering adalimumab formulation disclosed by Gokarn.

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 invalid 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 demonstrates that the challenged claims are anticipated by the Gokarn PCT under 35 U.S.C. §§ 102(a) and (e) (pre-AIA). 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 invalid for anticipation or, alternatively, for obviousness.

Second, Coherus has filed a petition demonstrating that the challenged claims are anticipated under 35 U.S.C. § 102(e) by U.S. Pub. No. 2016/0319011 ("Gokarn '011"). Gokarn '011 is prior art as of June 14, 2005—the filing date of the provisional application to which Gokarn '011 claims priority.

Third, Coherus has filed a petition demonstrating that the challenged claims are obvious over the 2003 Humira® Label in view of Fransson and the June 14, 2005 Gokarn '011 disclosure of bufferless formulations of high-concentration IgG1 antibodies.

Finally, Coherus has filed a petition demonstrating that the challenged claims are obvious over the 2003 Humira® Label in view of Fransson and high-concentration, 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' petitions rely on different 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 invalid 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:

	Lead Counsel	Backup Counsel
	E. Anthony Figg (Reg. # 27,195)	Joseph A. Hynds (Reg. # 34,627)
Email:	efigg@rothwellfigg.com	jhynds@rothwellfigg.com
Postal:	ROTHWELL, FIGG, ERNST & MANBECK, P.C. 607 14th Street, N.W., Suite 800 Washington, DC 20005	ROTHWELL, FIGG, ERNST & MANBECK, P.C. 607 14th Street, N.W., Suite 800 Washington, DC 20005
Hand Delivery:	Same as Postal	Same as Postal
Telephone:	202-783-6040	202-783-6040
Facsimile:	202-783-6031	202-783-6031

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 on the grounds listed in the table below. The ’619 patent is to be reviewed under pre-AIA law.

Ground No.	Description	102(e) Date	102(a) Date
Ground 1	Anticipation by the Gokarn PCT	June 8, 2006	Dec. 28, 2006
Ground 2 (alternative)	Obviousness over the Gokarn PCT in view of the Humira® label	June 8, 2006	Dec. 28, 2006

This petition asserts invalidity as of both the § 102(a) and § 102(e) dates listed in the table above. This petition is accompanied by the declaration of Klaus-Peter Radtke, Ph.D. (Ex. 1002) and copies of all exhibits relied on in the Petition and Declaration.

V. BACKGROUND

A. Adalimumab

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. 1001, claims 16-18; Ex. 1002 ¶¶ 56-57. Adalimumab, also known as D2E7, has been recognized for nearly two decades as an antibody with

promising therapeutic activity. Ex. 1002 ¶ 31. Adalimumab is the active agent in Humira®. Ex. 1002 ¶ 37. 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. 1005, 471; Ex. 1039, 3.

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. 1002 ¶¶ 37-39; Ex. 1005, 470; Ex. 1006, 13. The formulation included a phosphate / citrate buffering system, sodium chloride (an ionizable excipient), mannitol and polysorbate 80 (non-ionizable excipients), and water for injection. Ex. 1002 ¶ 38; Ex. 1005, 470; Ex. 1006, 13.

Adalimumab is a human IgG1 antibody. Ex. 1005, 470. All IgG antibodies have the same characteristic Y-shaped three-dimensional structure, and share highly homologous amino acid sequences. Ex. 1002 ¶¶ 32-35; Ex. 1007, 97**;** Ex. 1008, 178 ("Four IgG subclasses have been identified in both man and mouse which display >90% homology between their C-region domains."). Human IgG antibodies have an estimated 90-95% of amino acids conserved or identical across subclasses within their constant regions. Ex. 1002 ¶ 35; Ex. 1009, 111. The main source of variability among members of the IgG1 subclass is in the "hypervariable" complementarity determining regions (CDRs), which are

responsible for antigen specificity. Ex. 1002 ¶ 35; Ex. 1007, 96-97, 102-03, Fig. 7-4.

B. Buffer Systems

Independent claim 16 of the '619 patent covers *any* formulation of adalimumab in water without a "buffering system." Ex. 1001, 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. 1002 ¶ 43.

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. Ex. 1002 ¶¶ 42-44; Ex. 1010, 34; Ex. 1003, 28:21-23 ("Buffer capacity thus often is defined as the ability of a composition to resist pH change"). This ability to resist pH change comes from certain compounds in solution that have dissociable protons (e.g., weak acids and bases). Ex. 1011, 526; Ex. 1002 ¶ 43. The dissociation constant of an acid (its "pK_a value") is a measure of the strength of an acid in solution. Ex. 1002 ¶ 43. 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. 1002 ¶ 43; Ex. 1011, 527 (indicating that buffers are "most efficient" when pH = pK_a); Ex. 1012, 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. 1003, 3:3-4.

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. 1002 ¶ 44; Ex. 1003, 1:15-19, 2:9-20. 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. 1002 ¶ 44; Ex. 1003, 2:23-25 ("Buffers for pharmaceutical use … must not buffer so strongly that their administration deleteriously perturbs a subject's physiological pH"); Ex. 1013, 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.").

As the Gokarn PCT points out in its description of the background prior art, POSAs understood that traditional buffering systems "all have undesirable limitations and disadvantages. And they all have the inherent disadvantage of being an additional ingredient in the formulation, which complicates the

formulation process, poses a risk of deleteriously affecting other ingredients, stability, shelf-life, and acceptability to the end user." Ex. 1003, 3:5–8; Ex. 1002 ¶ 54.

C. Proteins as Buffers

POSAs have known for decades that a protein, by itself, can provide buffer capacity. Ex. 1002 ¶ 45; *see, e.g.*, Ex. 1010; Ex. 1011, 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. 1014, 715; Ex. 1010, 34. The 1966 paper entitled PROTEINS AS BUFFERS taught that the amino acids contributing to protein buffer capacity (over a wide pH range) included glutamic acid, aspartic acid, histidine, arginine, lysine, tyrosine, and cysteine. Ex. 1010, 34. 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. 1002 ¶ 43, 45; s*ee* Ex. 1010, 34, 36. In 1967, Nozaki and Tanford published the pK_as of the dissociable protons for various amino acids in peptide chains. Ex. 1014, 721; Ex. 1002 ¶ 47. This work demonstrates that aspartate (Asp), glutamate (Glu) and the imidazole group on histidine (His) contribute to a protein's buffer capacity in the pH range of about 4 to 6. Ex. 1002 ¶ 47; Ex. 1014, 721.

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. 1011, 539 ("It is evident . . . that the buffer effect . . . is proportional to the total molecular concentration [C] of the buffer."). Thus, a protein's buffer capacity will increase with protein concentration and also with the number of amino acids in each protein molecule that have dissociable protons with pK_a near the pH of the solution. Ex. 1002 ¶ 47; *see also* Ex. 1015, 749–50 (reference from 1994 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. 1014, 715 (1967); Ex. 1010, 34 (1966).

Most protein therapeutics do not contain a sufficiently high concentration of protein for the protein itself to provide sufficient buffering capacity. Ex. 1002 ¶ 48. Indeed, before November 2007, many commercially-available liquid therapeutic protein formulations had a low protein concentration (less than 15 mg/ml). Ex. 1002 ¶ 48; Ex. 1012, Appendix (IPR Pages 19-43). 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. 1002 ¶ 48. Accordingly, most commercially-available liquid therapeutic antibody formulations marketed as of November 2007 included a separate buffering system. *Id.*

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. 1002 ¶¶ 49-50. Many such immunoglobulin products are used to treat patients with immunodeficiency by providing a complete array of functional IgG antibodies. Ex. 1002 ¶ 50; Ex. 1016,925. Accordingly, the formulation must be effective for a wide variety of IgG antibodies, regardless of the antigen recognized by each antibody. Ex. 1002 ¶ 50.

An example of one such immunoglobulin product is Gamimune®. Ex. 1016. 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. 1002 ¶¶ 50-51; Ex. 1016, 925. About 98% of the protein in Gamimune was IgG antibodies. Ex. 1002 ¶ 50; Ex. 1016, 925. The remaining protein was mostly serum albumin, along with trace amounts of IgA and IgM antibodies. Ex. 1002 ¶ 50; Ex. 1016, 925. "The distribution of IgG subclasses is similar to that found in normal serum," (Ex. 1016, 925), meaning that about 65% of the IgG is of the IgG1 subclass, Ex. 1007, 101; Ex. 1002 ¶ 51. 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. 1016, 925; Ex. 1002 ¶ 52.

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. 1001, claim 16.

The '619 specification describes methods and compositions formulating proteins in water. Ex. 1001, 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. Ex. 1002 ¶¶ 57-59; *see, e.g.*, Ex. 1001, 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…"). The '619 patent notes that the omission of ionic excipients of all types (not just buffers) is particularly advantageous. *See, e.g.*, Ex. 1001, 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; 9:29-46. These techniques were well-known in the art. *See, e.g.*, Ex. 1001, 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. Ex. 1002 ¶ 59; Ex. 1001, 9:21-46; 22:44-24:3.

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. Ex. 1001, 3:37-42. In Example 1, for instance, an adalimumab formulation containing phosphate/citrate buffers, sodium chloride, and mannitol is diafiltered using a five-fold volume exchange with water to remove the excipients. 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 asserts that a wide-range of proteins (including antibodies) can be prepared in an excipient-free formulation. *See, e.g.*, Ex. 1001, 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).

Ex. 1001, 32:19-37. That is, the '619 patent asserts that a wide-range of proteins (not just adalimumab) can be prepared without an excipient and that adalimumab does not have any unique formulation requirements. *Id.*

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—approximately 11 months *after* the Gokarn PCT was published, and 18 months after the Gokarn PCT was filed. The Gokarn PCT was included in a list of nearly 300 references submitted to the Patent Office by AbbVie, but was never addressed by the Examiner during prosecution. *See* Ex. 1017, 212 (Information Disclosure Statement filed Oct. 3, 2014); *see also* Ex.1001, References Cited.

AbbVie first presented the challenged claims in a preliminary amendment filed November 21, 2014 in the '576 application. Ex. 1017, 293 (application claim

41 corresponds to issued claim 16). Prior to the filing of 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. 1018, 202–04, 271–73, 950–54, 1038–42; Ex. 1019, 4-14, 261-269, 1695-1704, 1735-1749; Ex. 1020, 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. 1002 ¶ 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. 1002 ¶¶ 59-60, 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. 1002 ¶¶ 59-60, 64-65; Ex. 1001, Example 1 (Col. 40 *et seq.*). 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. Ex. 1001, 10:61–63 ("[T]he total elimination of small molecules cannot be achieved in an absolute sense by DF/UF processing . . . ."); Ex. 1002 ¶ 65

(explaining that protein-solute interactions limit the ability to remove buffer components); Ex. 1021.

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. 1002 ¶ 65.

IX. PRIMARY REFERENCES RELIED UPON AND THEIR DATES OF AVAILABILITY AS PRIOR ART

A. The Gokarn PCT (Ex. 1003)

The Gokarn PCT application was filed internationally on June 8, 2006, designated the United States, and published in English on December 28, 2006. Ex. 1003. The Gokarn PCT application is the same as the Gokarn PCT publication in all relevant respects. Ex. 1003; Ex. 1022. The Gokarn PCT therefore is prior art under 35 U.S.C. § 102(e) at least as of its international filing date, June 8, 2006.[2] *EnOcean GmbH v. Face Int'l Corp.*, 742 F.3d 955, 957 n.3 (Fed. Cir. 2014) ("Since the … reference was filed on or after November 29, 2000, designated the

[2] The Gokarn PCT also claims priority to a provisional application filed June 14, 2005. Concurrently-filed petitions by Coherus demonstrate that the disclosure of the Gokarn provisional application (incorporated in Gokarn '011) also anticipates and renders obvious the challenged claims.

United States, and was published in English, it is available as prior art as of its PCT filing date.") (citing 35 U.S.C. § 102(e)(2)). The Gokarn PCT also is prior art under 35 U.S.C. § 102(a) as of the date of its publication, December 28, 2006. *See* 35 U.S.C. § 102(a).

The Gokarn PCT is entitled "self-buffering protein formulations." Ex. 1003, 1:1. The Gokarn PCT defines "self-buffering" as "the capacity of a substance, such as a pharmaceutical protein, to resist change in pH sufficient for a given application, in the absence of other buffers." *Id.* at 25:24–26. Put another way, a "self-buffering protein formulation" is the same as "a protein formulation that does not comprise a buffer system." Ex. 1002 ¶ 66.

Just as the '619 patent notes that its excipient-free formulations are applicable to a wide variety of proteins, the Gokarn PCT teaches a general method for formulating many different proteins without a traditional buffering system. Ex. 1002 ¶ 69 (*comparing* Ex. 1003, 51:15-52:8 *with* Ex. 1001, 32:8-37). The Gokarn PCT specifically identifies "HUMIRA (adalimumab)" as a protein to be used in the self-buffering formulations of the invention. Ex. 1003, 9:25. The Gokarn PCT also discloses a "particularly prefer[red]" concentration range of about 20-250 mg/mL, and an "especially particularly" preferred pH range of 4.0 to 5.5. Ex. 1003, 6:4-13.

Moreover, the Gokarn PCT claims a composition comprising 20–400 mg/ml of adalimumab and "one or more pharmaceutically acceptable polyols," wherein the "pH maintained by the buffering action of [adalimumab] is between approximately 3.5 and 8.0." *See, e.g.*, Ex. 1003, Claim 23 (incorporating the limitations of claims 9, 5, 4, 3, and 1, from which claim 23 ultimately depends).

B. 2003 Humira® Label (Ex. 1005)

The 2003 Humira® label has been available since Humira® entered the U.S. market in early 2003. Ex. 1005, 474; Ex. 1039, 3. It qualifies as prior art under 35 U.S.C. § 102(b), because it was publicly available more than one year prior to the '619 patent's earliest potential filing date of November 30, 2007. The label discloses that adalimumab is formulated at concentration of 50 mg/ml and a pH "of about 5.2." Ex. 1005, 470; Ex. 1002 ¶ 74. According to the Humira® label:

> Each 0.8 mL of HUMIRA contains 40 mg adalimumab, 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 0.24 mg sodium citrate, 1.04 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80 and Water for Injection, USP.

Ex. 1005, 470.

X. THE CHALLENGED CLAIMS ARE INVALID AS ANTICIPATED OR OBVIOUS IN VIEW OF THE GOKARN PCT

The challenged claims are invalid as anticipated by the Gokarn PCT. They also would have obvious over the Gokarn PCT in view of the 2003 Humira® label.

A. Ground 1: The challenged claims are anticipated by the Gokarn PCT (Ex. 1003).

The Gokarn PCT anticipates challenged claims 16-19 and 24-30 because it discloses every limitation of the challenged claims, arranged as in the claim. *See Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) ("A prior art reference can only anticipate a claim if it discloses all the claimed limitations 'arranged or combine in the same way as in the claim.'" (quoting *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012))).

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. 1001, claim 16; Ex. 1002 ¶ 76; *compare* Ex. 1001, SEQ ID Nos 3-8, *with* Ex. 1023, 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. 1001, claim 17; Ex. 1002 ¶ 86; *Compare* Ex. 1001, SEQ ID Nos 1-2, *with* Ex. 1023, SEQ ID Nos 1-2. Claim 18 depends from claim 17 and requires "wherein the antibody is adalimumab." Ex. 1001, claim 18; Ex. 1002 ¶ 86. 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 necessarily anticipate claims 16 and 17 as well. Claim 18 is therefore representative of claims 16-18.

1. The Gokarn PCT discloses every limitation of claim 18, arranged as in the claim.

The Gokarn PCT is entitled "Self-Buffering Protein Formulations." Ex. 1003, 1. Its Summary describes the invention as formulations "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* (i.e., other ingredients, if any, do not act substantially as buffering agents in the formulation)." *Id.* at 3:15-21 (emphasis added); *see also id.* at Abstract. The

Gokarn PCT's entire disclosure is therefore directed to formulations that "do not comprise a buffering system." Ex. 1002 ¶ 84.

The Gokarn PCT teaches that "[a]ny protein that provides sufficient buffer capacity within the required pH range at a concentration suitable for its intended use can be prepared as a self-buffering protein formulation." Ex. 1003, 27:4-7; *see also* Ex. 1003, 40:21-28. "HUMIRA (Adalimumab)" is specifically identified as a suitable protein for use in the self-buffering formulation. *Id.* at 9:25 and 51:24. Therefore, "a person of skill in the art, reading the [Gokarn PCT], would 'at once envisage' the claimed arrangement or combination" of adalimumab in an aqueous, buffer-free formulation. *Kennametal*, 780 F.3d at 1381 (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)); Ex. 1002 ¶ 79.

It is of no moment that the Gokarn PCT also teaches that other proteins could be formulated without a buffering system, because it clearly contemplates the use of adalimumab in an aqueous formulation that does not comprise a buffering system. Ex. 1002 ¶ 79, 84; *see Blue Calypso LLC v. Groupon Inc.*, 815 F.3d 1331, 1344 (Fed. Cir. 2016) (holding a reference anticipates if it "teaches that the disclosed components or functionalities may be combined and one of skill in the art would be able to implement the combination"); *see also Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1376 (Fed. Cir. 2005) (rejecting "the notion

that [a compound] cannot anticipate because it appears without special emphasis in a longer list"); *In re Gleave*, 560 F.3d 1331, 1336-38 (Fed. Cir. 2009) (same).

As detailed below, the Gokarn PCT discloses a formulation that meets every element of claim 18.

a. The Gokarn PCT discloses the preamble.

As an initial matter, Coherus does not concede that the preamble is limiting. Nonetheless, the Gokarn PCT discloses aqueous pharmaceutical formulations. Ex. 1002 ¶ 78. The abstract explains that "the invention provides self-buffering pharmaceutical protein formulations that are suitable for veterinary and human medical use." Ex. 1003, Abstract. The Gokarn PCT teaches that the formulations preferably include a liquid carrier, which preferably is "aqueous, most preferably [it is] largely or entirely comprised of pure water." *Id.* at 55:32-56:8.

b. The Gokarn PCT discloses adalimumab at a concentration of 50-200 mg/mL.

The Gokarn PCT identifies "HUMIRA (adalimumab)" as a suitable protein for use in its self-buffering compositions. Ex. 1003, 9:25, 51:24; Ex. ¶ 79. A POSA would have understood this disclosure to specifically teach the use of adalimumab at a concentration of 50mg/mL. Ex. 1002 ¶¶ 80-81. The Gokarn PCT does not simply refer to "adalimumab," but rather employs the trade name "HUMIRA" as well. Ex. 1003, 9:25. As of November 30, 2007, commercially-available "HUMIRA" was formulated at a concentration of 50 mg/mL and a pH of

5.2. Ex. 1002 ¶¶ 73-75, 81; Ex. 1005, 470; Ex. 1006, 13. Accordingly, a POSA would have understood the disclosure of "HUMIRA" to disclose adalimumab at a concentration of 50mg/mL.[3] Ex. 1002 ¶ 81. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991) (affirming finding of anticipation where extrinsic evidence demonstrated that a POSA would have understood the phrase "[Baxter] Travenol's commercial, two blood bag container" referred to a bag plasticized with DEHP).

This disclosure of 50 mg/mL adalimumab anticipates the claimed concentration range of 50-250 mg/mL. *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 869 (Fed. Cir. 2015) ("When a patent claims a range, as in this case, that range is anticipated by a prior art reference if the reference discloses a point within the range.").

Moreover, the Gokarn PCT expressly teaches that the concentration of the self-buffering protein is "particularly preferably between approximately 20 and

---

[3] As Dr. Radtke explains, a POSA also would have known that HUMIRA® included a phosphate/citrate buffering system. Ex. 1002 ¶ 81, n.1. However, because the Gokarn PCT is entirely directed to *self-buffering* protein formulations that "are substantially free of other buffering agents," (Ex. 1003, Abstract), a POSA would have understood the Gokarn PCT to teach omitting the buffering system from HUMIRA®, (Ex. 1002 ¶ 81, n.1).

250, especially particularly between approximately 20 and 150 mg/ml." Ex. 1003, 6:4-8. The Gokarn PCT also claims a composition comprising adalimumab, wherein the "concentration of the protein is between approximately 20 and 400 mg/ml." *Id.* at 84:18 (claim 23, incorporating the limitations of claims 5, 4, 3, and 1).

Therefore, even if "HUMIRA" were not a disclosure of 50mg/mL adalimumab, a POSA at least would have understood the Gokarn PCT to disclose adalimumab in a concentration range of 20-250 mg/mL, or 20-400 mg/mL, in a self-buffering formulation. Ex. 1002 ¶ 80. These concentration ranges encompass the range of 50 – 200 mg/mL required by claim 16 of the '619 patent. The '619 patent specification does not suggest that the range claimed in the '619 patent is critical to the operability of the alleged invention. Ex. 1002 ¶ 82. 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).

c. The Gokarn PCT discloses that the formulation comprises water.

The Gokarn PCT discloses that the self-buffering pharmaceutical formulations preferably include water. Ex. 1002 ¶¶ 71, 83; Ex. 1003, 55:32-56:8. Indeed, water is the only solvent specifically named in the Gokarn PCT. Ex. 1003,

55:32-56:8; Ex. 1002 ¶¶ 71, 83. Furthermore, a POSA would have understood that pharmaceutical protein formulations having a measureable pH are liquid formulations comprising water. Ex. 1002 ¶ 83.

d. The Gokarn PCT discloses that the formulation "does not comprise a buffering system."

As explained above, the crux of the Gokarn PCT's alleged invention is the absence of an extraneous buffering system. Ex. 1002 ¶¶ 66, 69, 84; Ex. 1003, Abstract, 3:16-21. The Gokarn PCT teaches the use of adalimumab in its self-buffering formulations—i.e., "in the absence of other buffers." Ex. 1002 ¶¶ 66, 69, 84; Ex. 1003, 9:25, 25:24-26, 51:24. The Gokarn PCT also teaches that in a most preferred embodiment, the protein (e.g., adalimumab) provides "at least approximately 99% of the buffer capacity of the composition." Ex. 1003, 5:30-6:3.

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. 1002 ¶¶ 64-65. The Gokarn PCT's disclosure of "self-buffering" protein formulations, and its disclosure of formulations in which the protein provides at least 99% of the buffer capacity, therefore satisfy the challenged claims' requirement that the formulation "does not comprise a buffering system." Ex. 1002 ¶¶ 64-65, 84.

2. The Gokarn PCT discloses 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. 1001, claim 19. 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 Gokarn PCT teaches that these same non-ionic excipients can be included in its self-buffering formulations. Ex. 1002 ¶ 88. Specifically, the formulation may comprise "one or more pharmaceutically acceptable polyols," such as "mannitol" or "sucrose." Ex. 1003, 6:24-30. The composition also may comprise a surfactant, such as "polysorbate 80." Ex. 1003, 6:31-34. Moreover, claim 23 of the Gokarn PCT depends from claim 9, which requires the formulation to include "one or more pharmaceutically acceptable polyols." Ex. 1003, 81:33-34. Polyols are non-ionizable excipients. Ex. 1002 ¶ 88. As evidenced by Claim 10, and the disclosure above, "pharmaceutically acceptable polyols" specifically include "sucrose" and "mannitol," which the '619 patent defines as non-ionizable excipients. Ex. 1003, 82:1-2; Ex. 1001, 10:1-3.

3. The Gokarn PCT discloses the pH ranges in claims 24-30.

As explained above in Section X.A.1, a POSA would have understood the Gokarn PCT's reference to "HUMIRA (adalimumab)" to disclose adalimumab at a concentration of 50mg/mL and a pH of 5.2, because as of November 30, 2007, all commercially-available "HUMIRA" was formulated at that concentration and pH. Ex. 1002 ¶¶ 73-75, 81, 94; Ex. 1005, 470; Ex. 1006, 13. 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).

Even if "HUMIRA" were not a disclosure of adalimumab at pH 5.2, the Gokarn PCT teaches a preferred pH for the self-buffering protein formulation of "between approximately . . . 4.0 and 6.0," and especially between "approximately 4.0 and 5.5." Ex. 1003, 6:9-13. These ranges anticipate the identical or broader ranges claimed in claims 24, 25, 27, and 28. *See, e.g.*, *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) (holding claimed range anticipated by a narrower range disclosed in the prior art).

The Gokarn PCT's preferred pH range of 4-6 also anticipates the somewhat narrower range of "from 5 to 6" in claims 26 and 29, and the pH of 5.2 in claim 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. 1002 ¶ 95; Ex. 1001, claims 24 and 27.

4. The Gokarn PCT is an Enabling Disclosure

The Gokarn PCT 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). AbbVie therefore would have the burden of showing that a POSA would not have been enabled to prepare the self-buffering adalimumab formulations disclosed by the Gokarn PCT. *Id.* This, AbbVie cannot do. The Gokarn PCT discloses the same diafiltration methods for preparing the self-buffering antibody formulations that are disclosed in the '619 patent. Ex. 1002 ¶¶ 64, 69; Ex. 1003, 70:3-15 ("[C]ompositions in accordance with the invention are prepared by a process that involves dialysis against a bufferless solution…."). Moreover, AbbVie has previously informed the Board that, by June 2005, a POSA already "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." Ex. 1024, 4 (citing Ex. 1025 and Ex. 1026).

5. Claim Chart Summarizing Anticipation by Gokarn PCT

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

'619 Patent Claim	**Gokarn PCT (Filed June 8, 2006)**
Claim 16. An aqueous pharmaceutical formulation comprising:	*The preamble is non-limiting.* "[T]he invention provides self-buffering pharmaceutical protein formulations that are suitable for veterinary and human medical use." Ex. 1003, Abstract.
(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,	"wherein the protein is selected from the group consisting of … HUMIRA (adalimumab) …." *Id.* at 9:15-25; *see also id.* at 51:24 & claim 23. Adalimumab comprises these sequences. *Compare* Ex. 1001, SEQ IDs, *with* Ex. 1023, SEQ IDs. This is further demonstrated by claim 18, 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	"HUMIRA (adalimumab)" discloses 50 mg/mL. Ex. 1002 ¶ 81. "[W]herein the concentration of the protein is between approximately… 20 and 200 …mg/ml." Ex. 1003, 6:5-6.

'619 Patent Claim	**Gokarn PCT (Filed June 8, 2006)**
	"[W]herein the concentration of the protein is between approximately 20 and 400 mg/ml." *Id.* at Claim 4.
(b) water;	"[F]ormulations of self-buffering proteins comprise a protein and a carrier. . . . In preferred embodiments . . . the carrier is a liquid. . . . Liquid carriers may be organic or non-organic. Preferably they are aqueous, most preferably are largely or entirely comprised of pure water." Ex. 1003, 55:32–56:8.
wherein the formulation does not comprise a buffering system.	"The self-buffering protein formulations are *substantially free of other buffering agents*…." Ex. 1003, Abstract (emphasis added). "'Self-buffering' means the capacity of a substance, such as a pharmaceutical protein, to resist change in pH sufficient for a given application, *in the absence of other buffers*." Ex. 1003, 25:24–26 (emphasis added). "the protein provides … very highly especially particularly preferably at least approximately 99% of the buffer capacity of the composition" Ex. 1003, 5:30-6:3. Claim 5 refers to "pH maintained by the buffering action of the protein . . . ."

'619 Patent Claim	**Gokarn PCT (Filed June 8, 2006)**
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.	"wherein the protein is selected from the group consisting of … HUMIRA (adalimumab) …." *Id.* at 9:15-25; *see also id.* at 51:24, claim 23. Adalimumab comprises these sequences. *Compare* Ex. 1001, SEQ IDs, *with* Ex. 1023, SEQ IDs. This is further demonstrated by claim 18, which is dependent on claim 17 and recites adalimumab. *See* 35 U.S.C. § 112, ¶4.
Claim 18. The formulation of claim 17, wherein the antibody is adalimumab.	"wherein the protein is selected from the group consisting of … HUMIRA (adalimumab) …." *Id.* at 9:15-25; *see also id.* at 51:24, claim 23.
Claim 19. The formulation of claim 16, wherein the formulation further comprises a non-ionizable excipient.	"one or more of sorbitol, mannitol, sucrose...." Ex. 1003, 6:24-30. "polysorbate 80." Ex. 1003, 6:34. Ex. 1003, Claim 23, which depends from claim 9 (requiring "one or more pharmaceutically acceptable polyols"). As evidenced by Claim 10, such polyols include mannitol and sucrose.
Claim 24. The formulation of claim 16, wherein the pH of the formulation is from 4 to 8.	"HUMIRA (adalimumab)" discloses pH 5.2. Ex. 1002 ¶ 94. Ex. 1003, Claim 23, which depends from claim 5 (requiring "the pH maintained by the buffering action of the protein is between approximately 3.5 to 8.")
Claim 25. The formulation of claim 16, wherein the pH of the formulation is from 4 to 6.	*See above for claim 24.* Further, "the pH maintained by the buffering action of the protein is between approximately … 4.0 to 6.0…." Ex. 1003, 6:9-11.

'619 Patent Claim	**Gokarn PCT (Filed June 8, 2006)**
Claim 26. The formulation of claim 16, wherein the pH of the formulation is from 5 to 6.	*See above for claims 24-25.* Further, the Gokarn PCT demonstrates that a variety of antibodies possess significant buffering capacity in the pH range 5.0 to 6.0. Ex. 1002 ¶ 92 (*discussing* Ex. 1003, Figs. 8, 11, 14B.)
Claim 27. The formulation of claim 18, wherein the pH of the formulation is from 4 to 8.	"HUMIRA (adalimumab)" discloses pH 5.2. Ex. 1002 ¶ 94. Ex. 1003, Claim 23, which depends from claim 5 (requiring "the pH maintained by the buffering action of the protein is between approximately 3.5 to 8.")
Claim 28. The formulation of claim 18, wherein the pH of the formulation is from 4 to 6.	*See above for claim 27.* Further, "the pH maintained by the buffering action of the protein is between approximately … 4.0 to 6.0…." Ex. 1003, 6:9-11.
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, the Gokarn PCT demonstrates that a variety of antibodies possess significant buffering capacity in the pH range 5.0 to 6.0. Ex. 1002 ¶ 92 (*discussing* Ex. 1003, Figs. 8, 11, 14B.)
Claim 30. The formulation of claim 18, wherein the pH of the formulation is 5.2.	*See above for claims 27-29.*

B. Ground 2: The challenged claims are obvious over the Gokarn PCT (Ex. 1003) in view of the 2003 Humira® label (Ex. 1005).

The challenged claims also are obvious over the Gokarn PCT in view of the Humira® label. The disclosure of the Gokarn PCT is prior art as of its filing date

for purposes of obviousness as well as for anticipation. *See Hazeltine Research, Inc. v. Brenner*, 382 U.S. 252, 256 (1965); *In re Bartfeld*, 925 F.2d 1450, 1451 n.4 (Fed. Cir. 1991) ("Though not anticipatory, a reference that would otherwise qualify as prior art under 35 U.S.C. § 102(e) may form the basis of an obviousness rejection under 35 U.S.C. § 103….").

Obviousness is a question of law based on underlying factual findings, including: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; (3) the differences between the claims and the prior art; and (4) secondary considerations of nonobviousness, such as commercial success, long-felt but unmet needs, failure of others, and unexpected results. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007); *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

As demonstrated in Section X.A., there are no meaningful differences between the Gokarn PCT's express teaching to use "HUMIRA (adalimumab)" in its self-buffering formulations, versus the aqueous formulations of adalimumab in claims 16-19 and 24-30 of the '619 patent that "[do] not comprise a buffering system." However, even if any of the challenged claims are not anticipated by the Gokarn PCT, they would have been obvious to a POSA. Ex. 1002 ¶¶ 97-105. Humira® was known in the prior art as an FDA-approved therapeutic IgG1 antibody (adalimumab) in a liquid formulation at a concentration of 50 mg/mL and pH of 5.2. Ex. 1002 ¶¶ 73-74, 99; Ex. 1005, 470. It would have been obvious to a

POSA to select the specific adalimumab concentration and pH known in the prior art, with an expectation of success in preparing a buffer-free formulation of adalimumab as taught by the Gokarn PCT. Ex. 1002 ¶¶ 97-105. The known concentration of 50 mg/mL and pH of 5.2 are within the scope of each and every challenged claim, and therefore render the challenged claims invalid for obviousness.

1. The 2003 Humira® Label teaches an aqueous pharmaceutical formulation comprising adalimumab at a concentration of 50 mg/mL and a pH of 5.2.

Long before November 2007, adalimumab was known as a pharmaceutical antibody useful for the treatment of rheumatoid arthritis. Ex. 1002 ¶¶ 31, 99; Ex. 1005, 470-471. Adalimumab has been commercially available in the United States since the commercial launch of Humira® in early 2003. Ex. 1002 ¶¶ 73-75, 99; Ex. 1039, 3. Humira® was formulated as an "aqueous pharmaceutical formulation." Ex. 1002 ¶ 99; Ex. 1005, 470, 472 (Humira® is provided in pre-filled syringe and stored at 2-8° C); Ex. 1005, 470 (Humira® further comprises "Water for Injection, USP").

The 2003 Humira® Label teaches that "[e]ach 0.8 mL HUMIRA contains 40 mg adalimumab . . . ." Ex. 1005, 470. This disclosure of 40 mg of adalimumab in 0.8 mL discloses the specific concentration 50 mg/mL adalimumab. Ex. 1002 ¶¶ 74, 99. "The solution of HUMIRA is clear and colorless, with a pH of about

5.2." Ex. 1005, 470. The Humira® label also teaches 50 mg/mL adalimumab in an aqueous solution with the non-ionic excipients mannitol and polysorbate 80. Ex. 1005, 470; Ex. 1002 ¶ 38.

2. A POSA would have been motivated to use the 50 mg/mL concentration and pH of 5.2 disclosed by the 2003 Humira® Label in the self-buffering adalimumab composition taught by the Gokarn PCT, with a reasonable expectation of success.

The Gokarn PCT identifies "HUMIRA (adalimumab)" as a protein for use in a self-buffering formulation. Ex. 1003, 9:25; Ex. 1002 ¶¶ 79, 84, 99. This disclosure of "HUMIRA" implicitly discloses to a POSA the 50 mg/mL concentration and pH of 5.2, and at a minimum directs the POSA to consider the Humira® formulation. Ex. 1002 ¶ 99; *see* Section X.A.1.b *supra*. To the extent any additional motivation— beyond the express teachings of the Gokarn PCT— was needed for a POSA to select a concentration of 50-200 mg/mL of adalimumab and a pH of 5.2, it is provided by the 2003 Humira® Label. Ex. 1002 ¶¶ 99-103.

A POSA would have been motivated to use a concentration and pH that were already used in an FDA-approved adalimumab commercial product. Ex. 1002 ¶¶ 100-103. A POSA would have understood from the 2003 Humira® Label that the optimal pH range for adalimumab had already been determined to be around 5.2. Ex. 1002 ¶ 103; Ex. 1012, 297 ("The stability of a protein drug is usually observed to be maximal in a narrow pH range."). The POSA also would

have found it obvious to use the same FDA-approved concentration of 50 mg/mL that already was known to be suitable for treatment of rheumatoid arthritis. Ex. 1002 ¶ 101; Ex. 1005, 470-71.

The POSA would have reasonably expected success in formulating adalimumab at 50 mg/mL and pH 5.2 without a buffering system, because the Gokarn PCT expressly discloses doing so. Ex. 1002 ¶¶ 101-103. The concentration of 50 mg/mL and the pH of 5.2 disclosed by the 2003 Humira® Label are squarely within the Gokarn PCT's particularly preferred concentration ranges (e.g., 20-250 mg/mL) and pH ranges (e.g., 4.0 to 5.5). Ex. 1003, 6:9-13.

Further, the Gokarn PCT teaches that its formulations are preferably applied to IgG antibodies (the class that includes adalimumab). Ex. 1003, 7:23; Ex. 1002 ¶ 104. Given the substantial identity of amino acid sequences and tertiary structures across all IgG antibodies, a POSA would have expected that different antibodies within the IgG class would have similar buffering capacity. Ex. 1002 ¶¶ 32-36, 104. The Gokarn PCT taught exactly that. Ex. 1002 ¶ 104; Ex. 1004, 3:1-8 (noting that the "total number of contributing charged amino acid residues" that create buffering capacity is "relatively constant for a given class of monoclonal antibodies"); Ex. 1003, 1:3-5 (incorporating by reference Ex. 1004).

The Gokarn PCT demonstrates that a variety of IgG antibodies, at a concentration of 50 mg/mL and formulation pH of about 5.2, possess sufficient

buffering capacity to obviate the need for an extraneous buffering system. Ex. 1002 ¶ 104 (citing Ex. 1003, Figs. 8, 11, 14). Based on these disclosures, a POSA would very reasonably have expected 50 mg/mL adalimumab to have sufficient buffering capacity to maintain a pH of 5.2 without the need for a traditional buffering system. Ex. 1002 ¶ 104.

Finally, as explained in Section X.A.4 above, a POSA would have known how to prepare the buffer-free formulations of adalimumab using techniques that were within a POSA's skill set. *See* Ex. 1003, 69:31-70:1 (teaching that "[r]esidual buffering agents can be removed … using a variety of well-known methods, including but not limited to, standard methods of dialysis and high performance membrane diffusion-based methods such as tangential flow diafiltration"); Ex. 1024, 4 (AbbVie statement that, by June 2005, 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"); Ex. 1002 ¶ 64 (diafiltration was a known technique).

3. Any secondary considerations are insufficient to overcome the strong prima facie case of obviousness

There are no secondary considerations that would overcome the strong evidence that the challenged claims are obvious over the Gokarn PCT in view of the 2003 Humira® Label. *See Pfizer v. Apotex*, 480 F.3d 1348, 1372 (Fed. Cir. 2007).

a. Unexpected Results

A POSA would have expected that 50–200 mg/ml of adalimumab would have had sufficient buffer capacity to be the sole source of pH control for a liquid formulation. Ex. 1002 ¶ 107. The Gokarn PCT explicitly stated this proposition. Ex. 1003, claim 23. And the Gokarn PCT demonstrated that various IgG antibodies have sufficient buffering capacity in the pH range of 4.0 to 6.0, when formulated at a concentration between 50 – 200 mg/mL, to provide the pH control for a liquid pharmaceutical formulation. Ex. 1002 ¶ 104; Ex. 1003, Figs. 8, 11, 14. A POSA would have understood that an antibody's buffer capacity was "approximately proportional" to the antibody concentration times its number of ionizable side chains, and further that the number of ionizable side chains remains "relatively constant for a given class of monoclonal antibodies." Ex. 1002 ¶ 108; Ex. 1004, 3:1–10. Adalimumab is a member of the same IgG class of antibodies as the exemplary antibodies in the Gokarn PCT, so a POSA would have expected it to display similar buffer capacity. Ex. 1002 ¶ 32, 34-35, 108. Thus, the buffering capacity demonstrated by 50-200 mg/ml adalimumab at a pH of 5.2 is precisely what a POSA would have expected.

b. Commercial Success

AbbVie held blocking patents on the D2E7 antibody that would have dissuaded others from developing alternative formulations of adalimumab during

the relevant timeframe. Ex. 1002 ¶ 109 (citing Ex. 1023, claim 28). "Where market entry by others was precluded due to blocking patents, the inference of non-obviousness of the asserted claims, from evidence of commercial success, is weak." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) (internal quotation marks and alterations omitted).

Moreover, any commercial success of Humira® cannot be attributed to the challenged claims. "'[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent.'" *Galderma*, 737 F.3d at 740 (quoting *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006)). Until late 2015, the only Humira® formulation approved by the FDA included a citrate-phosphate buffer system and was outside the scope of the challenged claims. Ex. 1002 ¶¶ 38-39, 110. By that time, Humira®'s yearly global sales were already far in excess of 10 billion USD. Ex. 1027, 5. Thus, any commercial success of Humira® cannot be credited to claims directed to a formulation that excludes a buffer system.

c. Long-Felt Need and Unmet Need

As with commercial success, any alleged long-felt need for buffer-free formulations of adalimumab is not probative of nonobviousness. To the extent that such need existed, competitors were not in a position to meet it by developing competing formulations because AbbVie held blocking patents, including a patent

claiming the adalimumab antibody ("D2E7") that did not expire until 2016. Ex. 1002 ¶ 109; *See Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376-77 (Fed. Cir. 2005) (explaining the rationale for finding nonobviousness based on secondary considerations may break down when "others were legally barred" from commercializing the invention); *Aventis Pharma S.A. v. Hospira, Inc.*, 743 F. Supp. 2d 305, 345 n.24 (D. Del. 2010) (discounting alleged long-felt need and failure of others where patentee held the prior art patent on the active ingredient of a drug, and therefore "formulators from other companies did not have a particularly powerful incentive to search for alternative formulations" of it), *aff'd* 675 F.3d 1324 (Fed. Cir. 2012).

Moreover, any need for a buffer-free adalimumab formulation had already been met by the Gokarn PCT's prior art disclosure. *See Newell Cos. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988) ("[O]nce another supplied the key element, there was no long-felt need or, indeed, a problem to be solved by [the patentee].").

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

/s/ E. Anthony Figg

E. Anthony Figg
Reg. No. 27,195
Joseph A. Hynds
Reg. No. 34,627
ROTHWELL, FIGG, ERNST
& MANBECK, P.C.
607 14th Street, N.W., Suite 800
Washington, DC 20005
Phone: (202) 783-6040
Fax: (202) 783-6031
Email: efigg@rfem.com
Email: jhynds@rfem.com

Attorneys for Petitioner

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 1002, 1005 and 1016, were served on counsel for Patent Owner via email (by consent), as follows:

Anthony M. Insogna
Tamera M. Weisser, Ph.D.
S. Christian Platt
Jones Day
12265 El Camino Real, Ste. 200
San Diego, CA 92130
Tel.: (858) 314-1200
Fax.: (858) 314-1150
Emails: aminsogna@jonesday.com
tmweisser@jonesday.com
cplatt@jonesday.com

David M. Maiorana (Reg. No. 41,449)
Jones Day
901 Lakeside Ave.
Cleveland, OH 44114
Tel.: (216) 586-3939
Fax.: (216) 579-0212
Email: dmaiorana@jonesday.com

Dated: April 10, 2017

/s/ Nasri V. B. Hage

Nasri V. B. Hage
ROTHWELL, FIGG, ERNST
& MANBECK, P.C.
607 14th Street, N.W., Suite 800
Washington, DC 20005
Phone: (202) 783-6040
Fax: (202) 783-6031
Emails: nhage@rfem.com
CoherusIPR619@rothwellfigg.com

CERTIFICATE OF COMPLIANCE

In accordance with 37 C.F.R. 42.24, as amended, the undersigned certifies that this Petition complies with the applicable type-volume limitations of 37 C.F.R. 42.24(a)(i). Exclusive of the portions exempted by 37 C.F.R. 42.24(a), this Petition contains 9,337 words as counted by the word processing program used for its preparation (Microsoft Word 2007).

Dated: April 10, 2017

/s/ E. Anthony Figg

E. Anthony Figg
Reg. No. 27,195
Joseph A. Hynds
Reg. No. 34,627
ROTHWELL, FIGG, ERNST
& MANBECK, P.C.
607 14th Street, N.W., Suite 800
Washington, DC 20005
Phone: (202) 783-6040
Fax: (202) 783-6031
Emails: efigg@rfem.com
CoherusIPR619@rothwellfigg.com

Attorney for Petitioner