IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

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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

(OBVIOUSNESS OVER THE 2003 HUMIRA® LABEL IN VIEW OF FRANSSON AND THE 2005 GAMIMUNE® LABEL)

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Regulations

LIST OF EXHIBITS

Exhibit No.	Document
1301	U.S. Patent No. 9,085,619, Fraunhofer et al.
1302	Declaration of Klaus-Peter Radtke, Ph.D.
1303	Declaration of David D. Sherry, M.D.
1304	Fransson & Espander-Jansson, "Local Tolerance of Subcutaneous Injections," J. Pharm. Pharmacol., 48:1012-1015 (1996)
1305	HUMIRA® Label (Jan. 2003)
1306	HUMIRA® Label (Jan. 2008)
1307	GAMIMUNE® Label (Oct. 2005)
1308	Christensen, "Proteins as buffers," Annals of the New York Academy of Sciences, 133:34-40 (Apr. 1966)
1309	Gelfand, "Differences Between IGIV Products: Impact on Clinical Outcome," Int'l Immunopharmacology, 6:592-99 (2006)
1310	Adalimumab Product Approval Information, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm080610.htm (accessed Jan. 23, 2017)
1311	AbbVie Biotechnology Ltd., "Annex A – The Humira® Story," in Opposition Proceeding for EP1406656 (filed on Dec. 22, 2014)
1312	U.S. Pub. No. 2003/0206898, Fischkoff et al.
1313	Jefferis et al., "Recognition Sites on Human IgG for Fcγ Receptors: The Role of Glycosylation," Immunology Letters, 44: 111-117 (1995)
1314	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)
1315	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)
1316	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)

Exhibit No.	Document
1317	Dean, "Lange's Handbook of Chemistry," McGraw-Hill, p 8.49, 8.65 (9th ed. 1999)
1318	U.S. Pub. No. 2003/0138417, Kaisheva et al.
1319	Laursen et al., "Pain Perception after Subcutaneous Injections of Media Containing Different Buffers," Basic & Clinical Pharmacology & Toxicology, 98:218–221 (2006)
1320	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)
1321	Nozaki & Tanford, "Examination of Titration Behavior," Methods Enzymol., 11: 715–734 (1967)
1322	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)
1323	Physicians' Desk Reference, pp. 558-59, 914-31, 805-07, 2026-28, 2295-97, 2524-25 (56th ed. 2002)
1324	McCue et al., "Three Generations of Immunoglobulin G Preparations for Clinical Use," Reviews of Infectious Diseases, 8:S374-81 (1986)
1325	Parslow, "Immunoglobulins & Immunoglobulin Genes," Ch. 7 in Medical Immunology, Appleton & Lange (Daniel P. Stites, Abba I. Terr, & Tristram G. Parslow eds., 9th ed. 1997)
1326	U.S. Prosecution History of App. No. 14/506,576 (U.S. Patent 9,085,619)
1327	U.S. Prosecution History of App. No. 13/774,735 (U.S. Patent 8,883,146)
1328	U.S. Prosecution History of App. No. 12/325,049 (U.S. Patent 8,420,081)
1329	U.S. Prosecution History of App. No. 61/004,992
1330	Stoner et al., "Protein–Solute Interactions Affect the Outcome of Ultrafiltration/Diafiltration Operations," J. Pharm. Sci., 93:2332–2342 (2004)
1331	U.S. Patent No. 6,090,382, Salfeld et al.
1332	OCTAGAM® Label (Mar. 2004)

Exhibit No.	Document
1333	"Injection Tips," Humira.com, http://www.humira.com/hu/hustore/cgi-bin/ProdSubEV_Cat_205043_SubCat_210170_NavRoot_205042_NavID_301.htm [http://web.archive.org/web/20050317083331/http://www.humira.com/hu/hustore/cgi-bin/ProdSubEV_Cat_205043_SubCat_210170_NavRoot_205042_NavID_301.htm (Archived Mar. 17, 2005)
1334	Gottlieb, "Efficacy and Safety of Anti-TNF-α Agents in Psoriasis," in Anti-TNF-α Therapies in the Treatment of Dermatologic Diseases at 6 (2005) (Supplement to Skin & Allergy News; Produced in Affiliation with the Skin Disease Education Foundation's 29th Annual Hawaii Dermatology Seminar)
1335	Schwartzman & Morgan, "Does Route of Administration Affect the Outcome of TNF Antagonist Therapy?," Arthritis Research & Therapy, 6(Suppl. 2):S19-S23 (2004)
1336	Granolleras et al., "Experience of Pain After Subcutaneous Administration of Different Preparations of Recombinant Human Erythropoietin: A Randomized, Double-Blind Crossover Study," Clinical Nephrology, 36:294-298 (1991)
1337	"Note for Guidance on Development Pharmaceutics," by the Committee for Proprietary Medicinal Products (CPMP), The European Agency for the Evaluation of Medicinal Products (Jan. 28, 1998)
1338	"Development Pharmaceutics for Biotechnological and Biological Products (Annex to Note for Guidance on Development Pharmaceutics)," by Committee for Proprietary Medicinal Products, The European Agency for the Evaluation of Medicinal Products (Oct. 21, 1999)
1339	GAMUNEX® Label (Nov. 2005)
1340	"Clinical Pharmacology and Biopharmaceutics Review(s)," by Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, Application No. 125057/0, in Approval Package for Humira® (Approved Dec. 31, 2002)
1341	"Fraunhofer Substantive Motion 3," in *Fraunhofer v. Gokarn*, Patent Interference No. 106,057 (filed on Oct. 12, 2016)
1342	Schwartz, "Diafiltration for Desalting of Buffer Exchange," BioProcess Int'l (May 2003)
1343	U.S. Pub. No. 2004/0033535, Boyle et al.

Exhibit No.	Document
1344	WO 1997/029131, Salfeld et al.
1345	HUMIRA® Label (Nov. 2015)
1346	HUMIRA® Label (Oct. 2016)
1347	SYNAGIS® Label (July 2004)
1348	Campath® Label (Aug. 2006)
1349	Vivaglobin® Label (Jan. 2006)
1350	CNJ-016 (Vaccinia Immune Globulin Intravenous) Label (Jan. 2010)
1351	GAMMAGARD LIQUID Label (April 2005)
1352	Flebogamma® Label (Jan. 2004)
1353	Privigen Label (Oct. 2016)
1354	HepaGam B™ Summary Basis for Approval (Jan. 2006)
1355	AVASTIN™ Label (Feb. 2004)
1356	TYSABRI® Label (Nov. 2004)
1357	Vectibix™ Label (Sept. 2006)
1358	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)
1359	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)
1360	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)
1361	U.S. Pub. No. 2016/0319011, Gokarn et al. ("Gokarn '011")
1362	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

Exhibit No.	Document
1363	van de Putte, et al., A Single Dose Placebo Controlled Phase I Study of the Fully Human Anti-TNF Antibody D2E7 in Patients with Rheumatoid Arthritis, Arthritis Rheum., 41(9), S57 (September 1998).
1364	HUMIRA® Label (Oct. 2005)
1365	HUMIRA® Label (Feb. 2008)
1366	HUMIRA® Label (Feb. 2007)
1367	HUMIRA® Label (Nov. 2006)
1368	Meadows & Hollowell, "'Off-label' drug use: an FDA Regulatory Term, Not a Negative Implication of Its Medical Use," Int'l J. Impotence Research 20:135-144 (2008)
1369	ENBREL® Label (Sept. 2002)
1370	ENBREL® Label (Nov. 1998)
1371	REMICADE® Label (Aug. 1998)
1372	Tsourounis, Biologic Therapies for the Treatment of Chronic Plaque Psoriasis, Formulary 40:184-199 (June 2005)
1373	U.S. Patent No. 6,696,056, Cheung et al.
1374	"Summary Review for Regulatory Action," by Sarah Yim, Division of Pulmonary, Allergy, and Rheumatology Products (U.S. Food & Drug Administration), of Humira® (2015)
1375	Nash, Randomized Crossover Comparison of Injection Site Pain with 40 mg/0.4 or 0.8 mL Formulations of Adalimumab in Patients with Rheumatoid Arthritis, Rhematol Ther 3:257-270 (2016)
1376	WO 2006/138181, Gokarn et al. (filed as PCT/US2006/022599)
1377	Handbook of Pharmaceutical Excipients, Pharmaceutical Press (Raymond C. Rowe, Paul J. Sheskey, & Siân C. Owen eds., 5th ed. 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. 1301). This petition and the accompanying declarations of Klaus-Peter Radtke, Ph.D. (Ex. 1302) and David Sherry, M.D. (Ex. 1303) demonstrate that claims 16-19 and 24-30 of the '619 patent (the "challenged claims") are unpatentable as obvious over the 2003 Humira® Label (Ex. 1305) in view of Fransson (Ex. 1304) and the 2005 Gamimune® Label (Ex. 1307). The 2003 Humira® Label, Fransson, and the 2005 Gamimune® Label were each published more than one year before the earliest possible priority date of the '619 patent, and therefore each reference is prior art under 35 U.S.C. § 102(b).

The challenged claims are obvious over the 2003 Humira® label in view of Fransson and the 2005 Gamimune® Label. There is **only one** difference between the challenged claims and the commercial adalimumab formulation disclosed by the 2003 Humira® label: the commercial Humira® formulation used a citrate-phosphate buffer, whereas the challenged claims "[do] not comprise a buffering system." This difference does not make the claims patentable.

A person of ordinary skill in the art ("POSA") would have been motivated to remove the citrate-phosphate buffer from the marketed Humira® formulation. A POSA would have known that pain on injection was a common side effect of

Humira®, and that this injection site pain was problematic for many patients. Further, a POSA would have known that Humira®'s citrate-phosphate buffer system was the most likely source of that pain. Fransson taught both that "citrate buffer causes pain" and that "for subcutaneous injections at non-physiological pH, the buffer strength should be kept as low as possible to avoid pain upon injection." Ex. 1304, 1012.[1]

To solve the problem of injection pain with Humira®, a POSA would have had two options: (1) use a different buffer system, or (2) remove the buffer system altogether. Both of these options were within a POSA's technical grasp and would have been obvious. Removing the buffer system altogether had the additional advantages of reducing the complexity of the formulation, improving process efficiency, reducing costs, simplifying regulatory compliance, reducing the potential for harmful interactions among formulation components, and reducing patient exposure to unnecessary excipients.

A POSA would have reasonably expected that the antibody in Humira® would provide sufficient buffer capacity to be the sole source of pH control for a

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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 1305, 1306, 1317, 1323, 1326-1329, 1332, 1333).

liquid pharmaceutical formulation at pH 5.2 (the pH of the Humira® formulation) in view of the 2005 Gamimune® Label. POSAs have known for decades that proteins can be self-buffering. *See, e.g.* Ex. 1308. Moreover, it was well known that the protein's buffering capacity increases as the protein concentration increases. *See id.* The 2005 Gamimune® Label demonstrates that a *high concentration of human IgG antibodies* (~50 mg/mL protein) possesses significant buffering capacity such that it can be formulated *without a separate buffering system*. Ex. 1302 ¶¶ 79, 97; Ex. 1307, 1-2.

Gamimune®, and other plasma-derived IgG products like it, were among the few high-concentration liquid pharmaceutical formulations of human IgG antibodies commercially available prior to November 30, 2007. These products deliver a wide variety of functional human IgG antibodies to treat immunocompromised patients. Thus, the formulation is effective for IgG antibodies regardless of the specific antigen that they recognize. Gamimune® and similar plasma-derived IgG products were formulated without a buffer system. *See* Ex. 1309, 597 (discussing various plasma-derived IgG products and stating "[a]s *the solutions are not buffered,* the pH is normalized on infusion and, as a result, has little or no consequence in the recipient") (emphasis added). Moreover, the absence of a buffer system was recognized as a benefit, because it minimized the

degree to which the formulation would affect the patient's physiologic pH. *Id.*; *see also* Ex. 1304, 1012.

A POSA would have looked to such existing high-concentration IgG products when formulating a high-concentration monoclonal antibody like adalimumab. Ex. 1302 ¶ 100-01, 106. The 2005 Gamimune® Label demonstrated that human IgG antibodies can be formulated at concentrations of about 50 mg/mL without a separate buffering system. POSAs knew that antibodies within the same class (e.g., all IgG antibodies) will all have very similar amino acid sequences and tertiary structure, and therefore very similar buffering capacity at a given concentration. In view of the 2005 Gamimune® Label's buffer-free 50 mg/mL IgG formulation, a POSA would have reasonably expected the IgG antibody in Humira® (i.e., 50 mg/mL adalimumab) to possess sufficient buffering capacity to maintain the formulation at a pH of 5.2.

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 obvious. 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 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).

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 invalid 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 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, because a POSA would

have "at once envisage[d]" each member of the small genus of high concentration liquid pharmaceutical antibodies, including 50 mg/mL adalimumab, as disclosed in the Gokarn Provisional for use in a bufferless formulation.

Finally, 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.

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 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:

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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 the email addresses above 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 of obviousness over the 2003 Humira® Label in view of Fransson and the 2005 Gamimune® Label. The '619 patent is to be reviewed under pre-AIA 35 U.S.C. § 103.

The 2003 Humira® Label, Fransson, and the 2005 Gamimune® Label were each published more than one year before November 30, 2007 (the earliest claimed priority date of the '619 patent). Each reference therefore is prior art under 35 U.S.C. § 102(b). This Petition is accompanied by the declarations of Klaus-Peter

Radtke, Ph.D. (Ex. 1302) and David Sherry, M.D. (Ex. 1303), and copies of all exhibits relied on in the Petition and Declaration.

V. BACKGROUND

A. Adalimumab and Humira

The challenged claims of the '619 patent are directed to formulations of the anti-tumor necrosis factor ("TNF") alpha antibody adalimumab, and closely-related antibodies. Ex. 1301, 152:16-39 (claims 16-18); Ex. 1302 ¶ 58. Adalimumab, also known as D2E7, has been recognized for nearly two decades as an antibody with promising therapeutic activity. Ex. 1302 ¶¶ 27-28. Adalimumab is the active agent in Humira®. Ex. 1302 ¶¶ 28-30. 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. 1302 ¶ 28; Ex. 1305, 4, 10; Ex. 1311, 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. 1302 ¶ 29; Ex. 1305, 1; Ex. 1306, 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. 1302 ¶ 29; Ex. 1305, 1; Ex. 1306, 13.

Injection site pain was a known problem with Humira®. Ex. 1303 ¶¶ 21-22, 28-30. The commercial label for Humira® reports that during clinical trials, 12% of patients taking Humira®, as well as 12% of patients taking the placebo formulation (i.e., the aqueous buffer system without the antibody), experienced injection site pain. Ex. 1303 ¶ 28; Ex. 1305, 8 (Table 4); Ex. 1312 ¶¶ 116-120. The fact that patients receiving placebo reported the same rate of injection pain as those receiving the active ingredient would have suggested to a POSA that the formulation components, rather than the adalimumab antibody, were the cause of the pain. Ex. 1302 ¶ 69; Ex. 1303 ¶¶ 28-30.

Adalimumab is a human IgG1 antibody. Ex. 1305, 1. All IgG antibodies have the same characteristic Y-shaped three-dimensional structure, and share highly homologous amino acid sequences. Ex. 1302 ¶¶ 33-35; Ex. 1325, 97. Human IgG antibodies are structurally homologous, with an estimated 90-95% of amino acids conserved or identical across subclasses within their constant regions. Ex. 1313, 111 ("Human IgG subclass proteins exhibit more than 95% primary amino acid sequence homology in their Fc regions…."); Ex. 1314, 178 ("Four IgG subclasses have been identified in both man and mouse which display >90% homology between their C-region domains."). Antibody sequences within each subclass (e.g., IgG1) are even more closely homologous. Ex. 1302 ¶¶ 35-36. 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. 1302 ¶ 35; Ex. 1325, 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. 1301, 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. 1302 ¶ 40.

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.* ¶ 40; Ex. 1308, 34. This ability to resist pH change comes from certain compounds in solution that have dissociable protons (e.g., weak acids and bases). Ex. 1315, 526; Ex. 1302 ¶ 40. The dissociation constant of an acid (its "pK_a value") is a measure of the strength of an acid in solution. Ex. 1302 ¶ 40. 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. 1302 ¶ 40; Ex. 1315, 527 (indicating that buffers are "most efficient" when pH = pK_a); Ex. 1316, 297 ("Ninety percent of the buffering capacity exists within one pH unit of its pK_a.").

Commonly-used buffering systems for protein pharmaceuticals include weak organic acids (e.g., acetate, succinate, citrate), certain amino acids (e.g., histidine), and phosphates. *See, e.g.*, Ex. 1361, 1 ¶ 9; Ex. 1316, 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. 1302 ¶¶ 41, 51, 83, 104; Ex. 1316, 299; Ex. 1309, 595-97; Ex. 1317, 5-6.

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. 1302 ¶¶ 37, 109; Ex. 1304, 1012 ("The purpose of buffers in pharmaceutical formulations is to maintain a stable pH, usually that at which the drug is most stable."); Ex. 1316, 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. 1302 ¶¶ 56, 76; Ex. 1304, 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. Buffer Systems Associated with Injection-Site Pain

Citrate and phosphate buffers were known to be associated with pain on injection. Ex. 1302 ¶¶ 53, 88; Ex. 1303 ¶¶ 32-35; Ex. 1318, 5 ¶ 50 ("Citrate and phosphate buffers are much less preferred because [they cause] a painful reaction when injected subcutaneously."); Ex. 1304, 1012 (reporting reduction in pain with lower concentration of phosphate buffer). It was particularly well known that citrate causes pain on injection. Ex. 1304, 1012 ("citrate buffer causes pain"); Ex. 1316, 297 ("[C]itrate is known to cause stinging upon injection."); Ex. 1319, 218 (comparing commercially-available human growth hormone formulations and concluding that the citrate buffered product caused significantly more pain on injection than the histidine-buffered product).

POSAs recognized that pain on injection is a serious problem because it sometimes prevents patients from taking the medication as prescribed. Ex. 1303 ¶¶ 23, 27, 32; Ex. 1319, 219 (stating that "[t]he benefit of minimizing the pain associated with subcutaneous injection of drugs is obvious" and noting that even short-term pain "may impair compliance"); Ex. 1320, 553 ("[L]ocal pain at the injection site is a common adverse event [for erythropoietin therapy], sometimes precluding self-administration.").

D. Proteins as Buffers

POSAs have known for decades that a protein, by itself, can provide buffer capacity. *See, e.g.*, Ex. 1308; Ex. 1315, 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. 1321, 715; Ex. 1308, 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. 1302 ¶¶ 41-42; s*ee* Ex. 1308, 34, 36. In 1967, Nozaki and Tanford published the pK_as of the dissociable protons for various amino acids in peptide chains. Ex. 1302 ¶ 98; Ex. 1321, 721. 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. 1302 ¶¶ 41-43, 98; Ex. 1321, 721.

POSAs understood that 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. 1302 ¶¶ 41-44; *see also* Ex. 1322, 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. 1321, 715; Ex. 1308, 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. 1302 ¶ 43; Ex. 1315, 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. 1302 ¶ 45. Indeed, before November 2007, the vast majority of commercially-available liquid therapeutic antibody formulations had a low protein concentration (less than 15 mg/ml). *Id.* ¶¶ 45, 106; Ex. 1316, Appendix (IPR Pages 19-43). A POSA would not have expected those low-concentration proteins to provide sufficient buffer capacity to be the *sole* source of pH control for such formulations. Ex. 1302 ¶ 45. 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 such as Gamimune® were formulated at high protein concentrations and without a separate buffering system. Ex. 1302 ¶¶ 47-52; Ex. 1309, 595-97. Many such immunoglobulin products are used to treat patients with immunodeficiency by providing a complete array of functional IgG antibodies. Ex. 1302 ¶ 48; Ex. 1307, 1 ("Gamimune® N, 5% supplies a broad spectrum of opsonic and neutralizing IgG antibodies for the prevention or

attenuation of a wide variety of infectious diseases."). Accordingly, the formulation must be effective for a wide variety of IgG antibodies, regardless of the antigen recognized by each antibody. Ex. 1302 ¶ 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 ¶ 52; *see, e.g.*, Ex. 1323, 14–16 (BayTet® product: enriched in anti-tetanus antibody, to treat tetanus exposure). A series of such products, enriched in antibodies to different antigens, can all employ the same concentration, formulation pH, and excipients. Ex. 1302 ¶ 52. As one example, the products BayHep®, BayRab®, BayRho®, and BayTet® are all formulated at a pH of 6.4 – 7.2, an antibody concentration of 150-180 mg/mL, and with the amino acid glycine as the sole excipient. Ex. 1302 ¶ 52; Ex. 1323, 6-16. Thus, BayHep®, BayRab®, BayRho®, and BayTet® all do not include a buffering system. Ex. 1302 ¶ 52; Ex. 1323, 6-16.

Gamimune® is an example of a non-specialized immunoglobulin product (i.e., it delivers a broad spectrum of antibodies, without enrichment for antibodies to a particular antigen). Ex. 1307, 1. 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. 1302 ¶ 49; Ex. 1307, 1. At least 98% of the protein in Gamimune® was IgG antibodies. Ex. 1302 ¶¶ 49, 77; Ex. 1307, 1; *see*

also Ex. 1324, S374 (reporting Gamimune® "is >99% IgG"). The remaining protein was mostly serum albumin, along with trace amounts of IgA and IgM antibodies. Ex. 1302 ¶ 77; Ex. 1307, 1. "The distribution of IgG subclasses is similar to that found in normal serum," (Ex. 1307, 1), meaning that about 65% of the IgG is of the IgG1 subclass, Ex. 1325, 101; Ex. 1302 ¶ 78. The Gamimune® label reports that "the buffer capacity of Gamimune® N, 5% is 16.5 mEq/L (~ 0.33mEq/g of protein)," demonstrating that POSAs understood that the concentrated protein itself provides the buffering capacity of the formulation. Ex. 1307, 2; Ex. 1302 ¶¶ 49, 79.

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. 1301, 152:16-32 (Claim 16).

The '619 specification describes methods and compositions formulating proteins in 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. Ex. 1302 ¶ 59; *see, e.g.*, Ex. 1301, 3:34-50, 10:57-61, 28:58-62 ("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. 1301, 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)."), *see also* 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))."); *see also* Ex. 1302 ¶ 60. DF and UF/DF employ a size exclusion filter that allows solvent and small-molecule excipients to pass through, but retains the protein. Ex. 1301, 9:21-50; 22:44-51; *see also* Ex. 1302 ¶ 60. 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. 1301, 9:21-46; 22:44-24:3; Ex. 1302 ¶ 60.

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. 1301, 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 asserts that a wide-range of proteins (including antibodies) can be prepared in an excipient-free formulation. *See, e.g.*, Ex. 1301, 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. 1302 ¶ 59.

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. Ex. 1301, 1:5-15 (Related Applications). Neither Fransson nor Gamimune® was before the Patent Office during prosecution of the '619 patent. Ex. 1301 (References Cited).

AbbVie first presented the challenged claims in a preliminary amendment filed November 21, 2014 in the '576 application. Ex. 1326, 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. 1327, 202–04, 271–73, 950–54, 1038–42; Ex. 1328, 4–14, 261–269, 1695–1704, 1735–49, 1868–88, 1946–69; Ex. 1329, 145–54.

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). Ex. 1302 ¶ 62-63. This person also would have had at least two years of experience preparing formulations of proteins suitable for therapeutic use. *Id*.

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. 1302 ¶¶ 65-66. 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. 1302 ¶¶ 60-61; Ex. 1301, 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. 1301, 10:61–63 ("[T]he total elimination of small molecules cannot be achieved in an absolute sense by DF/UF processing . . . ."); Ex. 1302 ¶¶ 61, 66 (explaining that protein-solute interactions limit the ability to remove buffer components); Ex. 1330, 2333-34, 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. 1302 ¶¶ 65-66.

IX. THE CHALLENGED CLAIMS ARE UNPATENTABLE AS OBVIOUS OVER THE 2003 HUMIRA® LABEL IN VIEW OF FRANSSON AND THE 2005 GAMIMUNE® LABEL

Obviousness is a question of law based on underlying factual findings, including: (1) "the level of ordinary skill in the pertinent art"; (2) "the scope and

content of the prior art"; (3) the "differences between the prior art and the claims at issue"; and (4) "secondary considerations" of nonobviousness, such as "commercial success, long felt but unsolved needs, failure of others," and unexpected results. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)).

A. Claims 16-18 Are Obvious Over the 2003 Humira® Label in View of Fransson and the 2005 Gamimune® Label

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. 1301, 152:15-33; Ex. 1302 ¶ 84; *Compare* Ex. 1301, SEQ ID Nos 3-8, *with* Ex. 1331, 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. 1301, 152:34-37; Ex. 1302 ¶ 113; *Compare* Ex. 1301, SEQ ID Nos 1-2, *with* Ex. 1331, SEQ ID Nos 1-2 . Claim 18 depends from claim 17 and requires "wherein the antibody is

adalimumab." Ex. 1301, 152:38-39; Ex. 1302 ¶ 113. 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).

1. The only difference between the 2003 Humira® Label and the challenged claims is the presence of a buffering system

The 2003 Humira® Label discloses an aqueous pharmaceutical formulation comprising 50 mg/mL adalimumab and water. Ex. 1302 ¶¶ 68, 85; Ex. 1305, 1 ("Each 0.8 mL of HUMIRA contains 40 mg adalimumab … and Water for Injection"). The 2003 Humira® Label discloses that the formulation contains a citrate-phosphate buffer. Ex. 1302 ¶¶ 68, 85; Ex. 1305, 1. As discussed in the following sections, it would have been obvious to a POSA to remove the citrate-phosphate buffering system to reduce injection pain and to simplify the formulation, and a POSA would have had a reasonable expectation of success in doing so.

The Supreme Court has instructed that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 550 U.S. at 421. If one of those known options "leads to the anticipated success, it is likely the product not of

innovation but of ordinary skill and common sense." *Id.* In other words, it is likely obvious. *Id.*

That is the situation here. A POSA would have been motivated to remove or replace Humira®'s buffer system, because Humira® causes pain on injection. Ex. 1302 ¶¶ 69, 86-89; Ex. 1303 ¶¶ 36-37. A POSA would have recognized that the citrate-phosphate buffer system was the likely cause of that pain. Ex. 1304, 1012; Ex. 1302 ¶¶ 88-89; Ex. 1303 ¶¶ 32-35, 38-41.

A POSA also would have recognized that the extraneous buffer system was unnecessary to control pH in a formulation containing a high concentration of IgG antibody (e.g., the 50 mg/mL adalimumab in Humira®), because Gamimune® and similar products were commercially available in aqueous, buffer-free formulations containing about 50 mg/mL IgG antibodies (i.e., 5% protein solution). Ex. 1302 ¶¶ 95-106; Ex. 1307, 1; Ex. 1332, 2. The 50 mg/mL protein in Gamimune® (98% of which is IgG) was known to impart so much buffer capacity that an extraneous buffering system would have been undesirable. Ex. 1302 ¶¶ 93-94; Ex. 1307, 2 (analyzing the ability of whole blood to neutralize the formulation); Ex. 1309, 597 ("As the solutions are not buffered, the pH is normalized on infusion, and, as a result, has little or no consequence in the recipient.").

A buffer-free formulation containing 50mg/mL of IgG antibody therefore was a known, technically feasible option. Ex. 1302 ¶¶ 47-52, 95-106; Ex. 1307, 1.

Applying a buffer-free formulation like that disclosed in the 2005 Gamimune® Label to 50 mg/mL adalimumab simply solved a known problem (pain due to buffer components) using a known solution (elimination of the extraneous buffer). Ex. 1302 ¶¶ 88-90, 94-95, 100-106. The buffer-free formulations of adalimumab claimed in claims 16-18 of the '619 patent therefore would have been obvious to a POSA. *See KSR*, 550 U.S. at 421.

2. A POSA would have been motivated to remove Humira®'s buffer system to reduce injection site pain

A POSA would have been motivated to remove Humira®'s buffer system, because Humira® caused pain on injection. A POSA would have understood that the most likely source of that pain was the citrate-phosphate buffer. Ex. 1302 ¶¶ 87-89; *see also* Ex. 1303 ¶¶ 32-35, 38-41.

The Humira® Label itself discloses, in Table 4, that 12% of patients reported injection site pain as an adverse event during clinical trials. Ex. 1305, 8. As Dr. Sherry points out, "this number is not the proportion of patients who experienced pain, but rather the percentage of patients who experienced pain to such a degree that they felt it necessary to report it." Ex. 1303 ¶ 28. The label also states that 12% of patients receiving placebo in Humira® clinical trials reported injection site pain. Ex. 1305, 8. POSAs knew that the pain associated with Humira® injections was more intense than just the discomfort associated with the penetration of the needle into the skin, and that the medication itself caused a

burning sensation. *See* Section IX.A.2.a *infra*. The fact that patients receiving placebo reported injection site pain at the same rate as patients receiving the active drug therefore informed the POSA that the cause of the pain was a formulation excipient rather than adalimumab itself. Ex. 1302 ¶¶ 69-71, 87; Ex. 1303 ¶ 28; Ex. 1312, ¶¶ 116-120, 149 (describing same 636-patient, 24-week clinical trial reported as "Study IV" in the 2003 Humira® Label, and stating placebo was "citrate-phosphate buffer solution without D2E7 [adalimumab]").

a. The pain associated with Humira® injections was known to be problematic for many patients

Although any subcutaneous injection may be uncomfortable (or even painful) to patients, the pain associated with injections of Humira® was known to be problematic for many patients. Ex. 1303 ¶ 26. As Dr. Sherry reports, for "approximately 10-20%" of his patients (who are primarily children), the injection site pain associated with Humira® made it difficult to adhere to the prescribed every other week injections. *Id.* at ¶¶ 22, 26-27.

Dr. Sherry's experience is consistent with literature reports and Humira® materials. For example, marketing materials for Humira® indicated that the penetration of the needle through the skin may cause slight pain or stinging, but that the medicine itself may cause a burning sensation. Ex. 1333, 1. Injection site pain also was recognized as a "major side effect" of Humira® in the literature. Ex.

1334, 8 ("The data from the phase II study for adalimumab demonstrated that injection-site pain was the major side effect with the use of that agent.").

The injection site pain associated with Humira® thus presented both patient discomfort and compliance issues. Painful injections are associated with decreased patient adherence, which presents a real problem for patient care. Ex. 1303 ¶¶ 23, 27; *see, e.g.*, Ex. 1335, S19 (Abstract) (stating that whether patients take the drug as directed is "possibly the most important factor in maintaining the benefits of anti-TNF therapy"); Ex. 1319, 218 (Abstract) ("Pain caused by subcutaneous injection is an unpleasant condition, which can limit patient compliance.").

The solution to this problem—removal of the citrate-phosphate buffering system—was widely known in the prior art.

b. The citrate-phosphate buffer in Humira® was the most likely cause of injection pain

Citrate buffers were well known to be associated with pain on injection. Ex. 1302 ¶¶ 53, 88; Ex. 1303 ¶¶ 32-35; Ex. 1304, 1012 ("citrate buffer causes pain"); Ex. 1319, 218 (teaching that citrate buffer causes significantly more pain on injection than histidine and saline); Ex. 1316, 297 ("[C]itrate is known to cause stinging upon injection."). One study, in particular, showed that a subcutaneous drug's citrate buffer caused enough pain on injection that it sometimes precluded self-administration of the drug. *See* Ex. 1320, 553 ("[L]ocal pain at the injection site is a common adverse event, sometimes precluding self-administration," and

"the local pain experienced after subcutaneous administration of epoetin alfa preparations is mainly caused by the citrate component of the buffered solution.").

Some reports also linked phosphate buffers to injection site pain. Ex. 1318, 5 ¶ 50 ("Citrate and phosphate buffers are much less preferred because [they cause] a painful reaction when injected subcutaneously."); *see* Ex. 1304, 1012. Fransson demonstrated that a high-concentration phosphate buffer system caused injection site pain when the formulation was administered at the non-physiological pH of 6. Ex. 1304, 1012 (Abstract). When the buffer capacity of the formulation was reduced, the pain was also reduced. *Id.* Fransson concluded that "for subcutaneous injection at non-physiological pH, the *buffer strength should be kept as low as possible to avoid pain upon injection*." *Id.* (emphasis added).

Fransson's teaching applies not only to the uniquely-painful citrate-phosphate buffer system, but more broadly, because a formulation that adjusts rapidly to normal physiologic pH also reduces pain. *Id.* ("[W]hen a non-physiologic pH must be used for stability reasons, a lower buffer strength enables more rapid normalization of the pH at the injection site."); Ex. 1302 ¶ 93. Given that the FDA-approved commercial formulation of adalimumab was administered at the relatively low pH of 5.2, a POSA would have known to reduce the buffering capacity as much as possible—including by eliminating extrinsic buffers—to reduce pain. Ex. 1302 ¶¶ 93-94.

While citrate and phosphate had been linked with pain on injection, a POSA would not have associated any of Humira®'s other excipients with pain on injection. Ex. 1302 ¶ 89. To the contrary, polysorbates, such as the polysorbate 80 in Humira®, had been linked with a ***reduction*** in pain on injection. *Id.*; Ex. 1336, 297. Therefore, a POSA would have known that Humira®'s citrate-phosphate buffer system was the most likely cause of the pain on injection. Ex. 1302 ¶ 89. As a result, a POSA would have been motivated to eliminate the citrate-phosphate buffer system. Ex. 1302 ¶¶ 87-89.

At most, a POSA had two predictable solutions available to reduce injection site pain caused by the citrate-phosphate buffer in HUMIRA: (i) identify a different extrinsic buffer system, or (ii) eliminate the extrinsic buffer and rely on the high (50 mg/mL or more) concentration of antibody to provide the formulation's buffer capacity. Ex. 1302 ¶ 90. Between these two choices, the POSA had many good reasons to eliminate the extrinsic buffer altogether, as discussed further below. Ex. 1302 ¶¶ 91-94.

3. A POSA would have been motivated to remove Humira®'s buffer system to eliminate unnecessary excipients

a. Regulatory authorities expect exclusion of unnecessary excipients

POSAs were well aware that unnecessary excipients should not be included in a pharmaceutical formulation. Ex. 1302 ¶ 91. As stated in a textbook chapter published in 2006 by Gokarn:

> In developing any formulation, excipients need to be selected *only when their use is essential* in imparting a desired pharmaceutical effect (i.e., stability or delivery). In fact, it is a regulatory expectation that an appropriate excipient be chosen and its level (amount) in a formulation be demonstrated and justified through formulation screening an development studies.

Ex. 1316, 294-95 (emphasis added); *see also* Ex. 1337, 3 (European regulatory guidelines requiring justification of excipients). Avoiding the use of unnecessary components is a matter of safety, because the potential always exists for adverse interactions among excipients or with the patient. Ex. 1302 ¶ 91; *see also* Ex. 1338, 3 ("Substantial evidence exists that proteins can interact chemically with the formulation excipients present in the finished product, for example, the formation of adducts which are potentially immunogenic."); Ex. 1316, 297 (discussing deleterious interactions with various buffer systems).

The 2005 Gamimune® Label demonstrates that an extraneous buffering system is not necessary in a high-concentration IgG formulation. Ex. 1302 ¶¶ 49, 94; Ex. 1307, 1. Moreover, the 2005 Gamimune® Label and Fransson both taught that excessive buffer capacity can even be deleterious when it affects the patient's physiological pH. Ex. 1302 ¶¶ 56, 76, 93-94. Fransson indicated that tissue damage, as well as pain, can result from excessive buffering capacity combined with an acidic formulation pH:

> At pH 6, a lower buffer concentration resulted in less discomfort, possibly because a higher buffer concentration results in a slower change in solution pH at the injection site. The frequency and intensity of occurring redness, paleness, and oedema at the injection site also decreased on reducing the buffer concentration….

Ex. 1304, 1014. The 2005 Gamimune® Label also reminds that the body's ability to neutralize the buffering capacity of the formulation upon administration must be taken into account. Ex. 1307, 2 (warning that "[i]n patients with limited or compromised acid-base compensatory mechanisms, consideration should be given to the effect of the additional acid load Gamimune N, 5% might present"); *see also* Ex. 1309, 597. A POSA thus would have understood that the extraneous citrate-phosphate buffer system in Humira® ideally should be removed, because it was

unnecessary and posed a risk of higher rates of adverse events and/or patient compliance issues. Ex. 1302 ¶¶ 93-94.

b. Elimination of unnecessary excipients streamlines processing and significantly reduces costs

A POSA also would have recognized that eliminating the extraneous buffering system from a 50 mg/mL adalimumab formulation would simplify manufacturing and quality control processes. As Dr. Radtke explains, the addition of an excipient requires additional controls and protocols to ensure that the excipient is satisfactory. Ex. 1302 ¶ 92. Further, a POSA would have understood that using fewer excipients can achieve significant cost savings. *Id.* Elimination of an excipient saves not only the cost of obtaining the excipient, but also production and employee costs associated with the steps to perform quality control and add the excipient to the formulation, as well as storage costs associated with maintaining inventory of the additional excipient. *Id.*

4. A POSA would have had a reasonable expectation of success in making the formulations of the challenged claims based on the 2005 Gamimune® Label

A POSA would have expected success in eliminating the citrate-phosphate buffering system from Humira® based on the 2005 Gamimune® Label. Ex. 1302 ¶¶ 95-100.

Gamimune® was marketed as an aqueous formulation that consists of 50 mg/mL protein—98% of which is human IgG antibodies—and maltose. Ex. 1307,

1; Ex. 1302 ¶¶ 49, 77, 79. Maltose is a sugar used as a tonicity modifier. Ex. 1302 ¶ 79; Ex. 1307, 1. It is not a buffer. Ex. 1302 ¶¶ 49, 79. The 2005 Gamimune® Label therefore describes an aqueous pharmaceutical formulation containing about 50 mg/mL of IgG antibodies and water which "does not comprise a buffering system." *See* Ex. 1301, claim 16; Ex. 1307, 1; Ex. 1302 ¶¶ 49, 77-79, 83, 95-97.

Gamimune® provides immunocompromised patients with *functional* human IgG antibodies that recognize a wide array of different antigens. Ex. 1302 ¶ 96; Ex. 1307, 1 ("Gamimune® N, 5% supplies a *broad spectrum* of opsonic and neutralizing IgG antibodies *for the prevention or attenuation of a wide variety of infectious diseases*.") (emphasis added). A POSA therefore would have recognized that a buffer-free formulation like Gamimune®'s would be suitable for a wide variety of high concentration IgG antibodies, including adalimumab. Ex. 1302 ¶ 96.

The 2005 Gamimune® Label reports the buffering capacity of the formulation as "~0.33 mEq/g of protein." Ex. 1307, 2. A POSA would have understood that the protein (98% IgG) imparted the buffer capacity to the formulation. Ex. 1302 ¶¶ 49, 79, 97. Indeed, it has been known for decades that proteins can act as buffers, and that a protein's buffer capacity is derived from certain of its amino acids (i.e., those that have dissociable protons with pK_as near the pH of the solution). Ex. 1302 ¶¶ 41-44, 98; *see generally* Ex. 1308; Ex. 1321,

721. It also was well known that buffer capacity increases as the concentration of the buffering species increases. Ex. 1302 ¶¶ 43-44, 100; Ex. 1315, 539. Thus, a POSA would have expected that proteins with similar amino acid sequences and configurations would have similar buffering capacity at a given concentration. Ex. 1302 ¶¶ 98-100.

POSAs knew that the amino acid sequences and tertiary structure of human IgG antibodies are very similar. Ex. 1302 ¶¶ 33-36, 99-100. Indeed, the amino acid sequences of human IgG antibodies are an estimated 90-95% homologous across their constant regions. Ex. 1302 ¶¶ 35, 99; Ex. 1314, 178 (1991) ("Four IgG subclasses have been identified in both man and mouse which display >90% homology between their C-region domains."); Ex. 1313, 111 ("Human IgG subclass proteins exhibit more than 95% primary amino acid sequence homology in their Fc regions…."). A person of ordinary skill in the art would have recognized that the protein in Gamimune® (which is 98% human IgG antibodies, approximately 65% of which are IgG1) and adalimumab (the human IgG1 antibody in Humira®) would have very similar amino acid sequences. Ex. 1302 ¶¶ 36, 99; Ex. 1307, 1; Ex. 1325, 101.

Accordingly, the POSA would have understood that 50 mg/mL of adalimumab (a human IgG antibody) would have a very similar buffering capacity to the 50 mg/mL of human IgG antibodies in Gamimune®. Ex. 1302 ¶¶ 99-100.

This expectation also would have applied at the higher concentrations (up to 200 mg/ml) of the challenged claims, because buffer capacity is known to increase with concentration. Ex. 1302 ¶ 105; Ex. 1315, 539.

Gamimune®'s ample buffering capacity controlled the formulation pH without the need for an extraneous buffering system. Ex. 1302 ¶¶ 79, 83, 94-97; *see* Ex. 1307, 1. A POSA therefore would have appreciated that the extraneous buffer system in Humira® was unnecessary to control the formulation pH, because the high concentration of IgG antibody (i.e., 50 mg/mL adalimumab) would have sufficient buffering capacity to do so. Ex. 1302 ¶¶ 98-100.

In 2006, the Gamimune® product line was replaced by Gamunex®. Ex. 1302 ¶ 82; Ex. 1309, 599. Gamimune® was replaced by Gamunex® for reasons unrelated to its formulation or stability. Ex. 1302 ¶¶ 82-83. In fact, Gamimune® 10% and Gamunex® have the same formulation: 9-11% protein (> 98% IgG) in 0.16-0.24M glycine. Ex. 1302 ¶ 82; Ex. 1323, 19; Ex. 1339, 1. Rather, Gamunex® reflects an improved process to prepare the IgG, including the steps used to ensure that the product is free of viruses that could infect the patient. Ex. 1302 ¶ 82; Ex. 1309, 599; *see* Ex. 1339, 1-3 (discussing process and reporting clinical trial results indicating Gamunex® displayed improved efficacy compared to Gamimune®). Accordingly, a POSA would have understood that Gamimune®,

which had been marketed since at least 1986, was a stable liquid formulation of 50 mg/mL human IgG antibody. Ex. 1302 ¶¶ 78-79, 83; *see* Ex. 1324, S374.

The product (Gamunex®) that replaced Gamimune® also demonstrates that a high-concentration, liquid formulation of human IgG antibodies could be formulated without a buffering system. Ex. 1302 ¶¶ 83,104. Gamunex® is a 10% protein formulation (i.e., 100 mg/mL), of which not less than 98% is human IgG antibodies. Ex. 1339, 1. The only excipient it contains is 0.16-0.24M glycine. *Id.* Glycine is used as a stabilizer and isotonicity modifier. *Id.* at 1, 5. At the pH of Gamunex® (pH 4.0-4.5), *id.* at 1, glycine does not act as a buffer, Ex. 1302 ¶¶ 83, 104.

Additionally, Gamimune® was not the only prior art IgG product that was successfully formulated at a concentration of 50 mg/mL without a buffering system. A POSA would have known that such immune globulin products were formulated without a separate buffering system across a range of different pH values. Ex. 1302 ¶¶ 47-52, 101-103. For example, in addition to Gamimune® (formulated at pH 4-4.5), Octagam® comprised 50 mg/mL of protein (96% of which was IgG) and 100 mg/mL of maltose in water for injection. Ex. 1332, 2; Ex. 1309, 596; Ex. 1302 ¶¶ 50, 103. Maltose, which is also present in Gamimune®, is a sugar (i.e., a non-ionizable excipient) used as a tonicity modifier. Ex. 1302 ¶¶ 50, 79, 103. Octagam® does not comprise a buffer system. Ex. 1302 ¶¶ 50, 103;

Ex. 1332, 2; *see also* Ex. 1309, 597 (describing commercially available plasma-derived human IgG products, including Octagam®, and noting that "the solutions are not buffered"). Octagam® was formulated at a pH of 5.1—6.0, and had a shelf-life of 24 months as a liquid formulation. Ex. 1309, 596. A POSA therefore would have expected that a human IgG antibody, at a concentration of about 50 mg/mL or higher, could provide sufficient buffer capacity without a separate buffer system across a range of pH values around Humira®'s pH of 5.2. Ex. 1302 ¶¶ 102-103. Thus, a POSA would have known from the 2005 Gammimune® Label and the state of the art regarding human plasma-derived immunoglobulin products, as reflected by products such as Gamunex® and Octagam®, that stable high-concentration IgG formulations could be prepared without the use of a separate buffering system. *Id.* ¶¶ 102-106.

Moreover, the absence of a buffer system in the various plasma-derived human IgG products was known to be beneficial, because it minimized changes to the patient's physiological pH. Ex. 1302 ¶¶ 56, 76, 81, 93-94; Ex. 1307, 2 (explaining that Gamimune®'s buffer capacity is sufficiently low that the formulation is rapidly neutralized by the blood); Ex. 1309, 597 (noting the acidic pH used in intravenous IgG products and explaining that "[a]s *the solutions are not buffered*, the pH is normalized on infusion and, as a result, has little or no consequence in the recipient") (emphasis added).

Before November 2007, there were relatively few commercially-available liquid formulations of pharmaceutical antibodies at high concentrations. Ex. 1302 ¶ 106; Ex. 1316, Appendix (IPR Pages 19-43). Other than Humira® and two other monoclonal antibodies, Synagis® (100 mg/mL palivizumab) and Campath® (30 mg/mL alemtuzumab), the various plasma-derived human IgG products were the only FDA-approved liquid formulations containing IgG antibodies at concentrations of about 50 mg/mL or higher. Ex. 1302 ¶¶ 31, 106. The absence of an extraneous buffering system in multiple high-concentration liquid formulations of plasma-derived human IgG antibodies would have given the POSA a reasonable expectation of success in formulating the IgG antibody adalimumab at a high concentration (e.g., 50-200 mg/mL) without an extraneous buffering system. *Id.* ¶¶ 95-96, 100-106. The fact that the *low-concentration* therapeutic protein formulations commercialized prior to November 2007 had almost always included a separate buffering system would not have dissuaded the POSA from preparing a *high-concentration* antibody product without a buffering system, because it was well-known that the protein concentration determines its buffering capacity. Ex. 1302 ¶¶ 41-44, 106; Ex. 1315, 539; Ex. 1322, 749–50.

The fact that the FDA-approved formulation of adalimumab included a buffer system also would not have detracted from a POSA's expectation of success in removing it. Ex. 1302 ¶¶ 106-107. The initial formulation of a therapeutic often

is established relatively early during development because of the necessity for long-term stability studies. *Id.* ¶ 107. In Humira®'s case, most clinical trials of adalimumab were conducted using lower antibody concentrations at which the separate buffer system may have been desirable or expedient. *Id.*; Ex. 1340, 60. Once the 50 mg/mL concentration was selected for the commercial formulation, it would have been significantly faster and simpler to adopt the same or similar formulation that was used in clinical studies and had stability data, than to develop and test a brand new formulation. Ex. 1302 ¶ 107. However, after the launch of Humira at 50 mg/mL, a POSA would have reasonably expected success in formulating it without a separate buffer, because Gamimune® (and other IgG products like it) had been formulated at concentrations of 50 mg/mL without an extraneous buffering system. Ex. 1302 ¶¶ 100-104, 107.

A POSA also would have expected that a buffer-free 50 mg/mL adalimumab formulation at a pH of 5.2 would be stable. The fact that adalimumab already was known to be stable in a 50 mg/mL aqueous formulation at pH 5.2 (*i.e.*, in Humira®) means a POSA would have reasonably expected a buffer-free 50 mg/mL aqueous formulation at 5.2 to be stable, because the high concentration antibody would maintain the pH of the formulation. Ex. 1302 ¶¶ 109-111. Gamimune® and Octagam® were both available as stable liquid formulations at 50 mg/mL protein (nearly all of which is human IgG antibodies), at pH values of

about 4.0-4.5 and 5.1-6.0, respectively. Ex. 1302 ¶¶ 78-79, 83, 95, 103, 110; Ex. 1309, 596 (Octagam®); Ex. 1307, 1. A POSA therefore would have reasonably expected the human IgG antibody adalimumab, at a concentration of 50 mg/mL, to provide sufficient buffering capacity to maintain a formulation pH of 5.2.

POSAs recognized that formulating a protein at the optimal pH is an important consideration for preparing a stable formulation. Ex. 1302 ¶ 109; *see, e.g.* Ex. 1316, 297 ("The stability of a protein is usually observed to be maximal in a narrow pH range."); *id.* at 294 ("[T]he most significant formulation variable, with respect to the rates of the [chemical degradation] reactions, is the solution pH."). Selection of an appropriate pH can reduce both physical instability (e.g., aggregation) and chemical instability (e.g., hydrolytic degradation). Ex. 1302 ¶ 109; Ex. 1316, 293-94.

The pH of 5.2 had already been demonstrated to provide sufficient stability for adalimumab, including at the concentration of 50 mg/mL. Ex. 1302 ¶ 110; *see* Ex. 1305, 1. A POSA would have reasonably expected success in using high-concentration adalimumab to maintain the formulation at a pH of 5.2, and adalimumab was known to be stable at that pH. Ex. 1302 ¶ 110. Indeed, eliminating the extraneous buffer system would have been expected to reduce the potential for certain chemical degradation reactions. Ex. 1302 ¶ 111; Ex. 1316,

294 ("[B]uffer salts have been shown to catalyze deamidation reactions….") (citing three articles published in 1990).

Moreover, POSAs knew that excipients other than the buffering system could assist in stabilizing the protein. Ex. 1302 ¶ 111; Ex. 1316, 293. For example, formulators use "excipients such as polyols and sugars [to] help maintain a protein in its more compact native state," preventing aggregation. Ex. 1302 ¶ 111; Ex. 1316, 293. Surfactants (e.g., polysorbate 80) are used to "inhibit surface-induced aggregation phenomena." Ex. 1302 ¶ 111; Ex. 1316, 293. The challenged claims do not exclude the presence of any of these stabilizer molecules. *See* Ex. 1301, 152 (claims 16-19 and 24-30).

A POSA also would have reasonably expected success in preparing the buffer-free 50 mg/mL adalimumab formulation. As AbbVie has admitted, 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. 1341, 4 (citing Ex. 1342 and Ex. 1343).

An aqueous formulation comprising 50-200 mg/mL adalimumab and water, without a buffering system, would have been obvious to a POSA based on the combined teachings of the 2003 Humira® Label, Fransson, and the 2005 Gamimune® Label. Ex. 1302 ¶¶ 84-112. A POSA would have readily combined Fransson's strategies to reduce pain on subcutaneous injection to solve the problem

of injection site pain identified in the 2003 Humira® Label. Ex. 1302 ¶¶ 69, 86-89, 93. A POSA also would have been motivated to combine the Humira® and Gamimune® formulations, because both products are liquid pharmaceutical formulations for IgG antibodies at a concentration of 50 mg/mL. Ex. 1302 ¶¶ 77-83, 94-95. A POSA also would have recognized that the buffer-free formulation of Gamimune® would elegantly conform with Fransson's guidance to avoid citrate and reduce the buffering capacity of a formulation to reduce injection site pain. Ex. 1302 ¶¶ 87-89, 93-96; Ex. 1304, 1012.

B. Claim 19 of the '619 Patent Is Obvious Over the Humira® Label in view of Fransson and the 2005 Gamimune® Label

Claim 19 recites "[t]he formulation of claim 16, wherein the formulation further comprises a non-ionizable excipient." Ex. 1301, 152:40-41. Gamimune®'s formulation includes maltose, Ex. 1307, 1, which is defined by the '619 patent as a non-ionic excipient, Ex. 1301, 10:1-3. The FDA-approved Humira® formulation contains mannitol and polysorbate 80, both of which are non-ionizable excipients. *Id.*; Ex. 1305, 1; Ex. 1302 ¶ 29.

It would have been obvious to a POSA that these non-ionic excipients could remain in place if so desired when removing the citrate-phosphate buffer system from Humira®. Ex. 1302 ¶¶ 115-117. These other excipients would not have been expected to contribute to injection site pain. *Id.*; *see* Ex. 1316, 296 (Table 1).

Claim 19 of the '619 patent therefore would have been obvious over the Humira® Label in view of the 2005 Gamimune® Label.

C. Claims 24-30 of the '619 Patent Are Obvious Over the Humira® Label in view of Fransson and the 2005 Gamimune® Label

Claims 24 and 27 depend from claims 16 and 18, respectively, and require that "the pH of the formulation is from 4 to 8." Ex. 1301, 152. Claims 25 and 28 depend from claims 16 and 18, respectively, and require that "the pH of the formulation is from 4 to 6." Ex. 1301, 152. Claims 26 and 29 depend from claims 16 and 18, respectively, and require that "the pH of the formulation is from 5 to 6." Ex. 1301, 152. Claim 30 depends from claim 18 and requires that the pH is 5.2. Ex. 1301, 152.

The 2003 Humira® Label taught that the product was formulated at a pH of 5.2. Ex. 1305, 1. A POSA would have recognized that this is a favorable formulation pH for adalimumab, and would have found it obvious to use the same pH for a buffer-free adalimumab formulation. Ex. 1302 ¶ 110, 120. As discussed in Section IX.A.4 above, a POSA would have had a reasonable expectation of success that 50 mg/mL adalimumab would possess sufficient buffer capacity to maintain the formulation at a pH of 5.2. Ex. 1302 ¶¶ 102-103, 109-111, 120.

The pH of 5.2 falls within the ranges recited in each of claims 24-29, and is the same pH recited in claim 30. The '619 patent gives no indication that any of the claimed ranges are critical, and therefore claims 24-30 are all obvious over the

2003 Humira® Label in view of Fransson and the 2005 Gamimune® Label. *See, e.g.*, *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) ("The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. These cases have consistently held that … the applicant must show that the particular range is *critical*....") (internal citations omitted) (emphasis in original).

X. 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 2003 Humira® Label in view of Fransson and the 2005 Gamimune® Label. *See Pfizer v. Apotex*, 480 F.3d 1348, 1372 (Fed. Cir. 2007).

A. Unexpected Results

There are no unexpected results here. 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, and therefore that "buffer-free" formulations were not only feasible, but completely expected. Ex. 1302 ¶ 123. Gamimune® and similar plasma-derived IgG products demonstrated that human IgG antibodies can be formulated at concentrations of about 50 mg/mL without a separate buffering system. Ex. 1302 ¶¶ 95-106; Ex. 1307, 1; Ex. 1332, 2. POSAs

knew that IgG antibodies share extensive amino acid sequence homology and tertiary structure, and therefore would have expected different human IgG antibodies to have about the same buffering capacity at a given concentration. Ex. 1302 ¶¶ 33-36, 99-100, 123; Ex. 1314, 178. 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.

Further, as stated in Section IX.A.4 above, a POSA would have expected the buffer-free formulation to be stable because 50 mg/mL adalimumab at a pH of 5.2 was known to be stable, and the antibody itself was expected to maintain the formulation pH. Ex. 1302 ¶¶ 109-111, 123.

To the extent AbbVie would argue that the reduction of pain was an unexpected result, it was not. As detailed in Section IX.A.2, a POSA would have expected that removing the citrate-phosphate buffer from the Humira® formulation would reduce injection site pain because both citrate and high buffer capacity in general were known to contribute to pain. Ex. 1302 ¶ 124; Ex. 1303 ¶¶ 32-34; *see,e.g.*, Ex. 1304, 1012.

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. 1302 ¶ 125 (citing Ex. 1331 at 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. 1302 ¶ 126. By that time, Humira®'s yearly global sales were already far in excess of 10 billion USD. Ex. 1311, 4. Thus, any commercial success of Humira® cannot be credited to claims directed to a formulation that excludes a buffer system.

C. Long-Felt 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 that claiming the adalimumab antibody ("D2E7") that did not expire until 2016.

Ex. 1302 ¶ 125; Ex. 1331, claim 28. Those patents prevented others from commercializing any adalimumab formulation. *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 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 alleged need for buffer-free antibody formulations had already been met by Gamimune® and similar plasma-derived IgG products. *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 of 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: January 31, 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 January 31, 2017, a complete and entire copy of the foregoing Coherus BioSciences Inc.'s Petition for *Inter Partes* Review of U.S. Patent No. 9,085,619, along with supporting exhibits and Power of Attorney, were provided via U.S.P.S. Priority Mail Express, costs prepaid, to the Patent Owner by serving the following correspondence address of record:

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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 10,379 words as counted by the word processing program used for its preparation (Microsoft Word 2007).

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