IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

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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 2003 HUMIRA® LABEL IN VIEW OF FRANSSON AND GOKARN '011; OBVIOUSNESS OVER GOKARN '011 IN VIEW OF 2003 HUMIRA® LABEL)

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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. 1201). This petition and the accompanying declarations of Klaus-Peter Radtke, Ph.D. (Ex. 1202) and David Sherry, M.D. (Ex. 1207) demonstrate that claims 16-19 and 24-30 of the '619 patent (the "challenged claims") are obvious over 1) the 2003 Humira® Label (Ex. 1205) in view of Fransson (Ex. 1219) and U.S. Publication No. 2016/0319011 ("Gokarn '011," Ex. 1203) and 2) Gokarn '011 in view of the 2003 Humira® Label. Gokarn '011 properly claims priority to, and incorporates by reference, U.S. Provisional Application No. 60/690,582, filed June 14, 2005 (the "Gokarn Provisional," Ex. 1204). Gokarn '011 therefore is prior art under 35 U.S.C. § 102(e) as of its June 14, 2005 effective filing date.

The challenged claims are obvious over the 2003 Humira® label in view of Fransson and Gokarn '011 as of June 14, 2005. 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.

By June 14, 2005, 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 from the 2003 Humira® Label 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. 1219, 1012.[1]

To solve the known 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. Eliminating 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

[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 1206, 1226-1230, 1237, 1271, 1272).

potential for harmful interactions among formulation components, and reducing patient exposure to unnecessary excipients.

A POSA would have reasonably expected that the high antibody concentration in Humira® would provide sufficient buffer capacity to be the sole source of pH control for a liquid pharmaceutical formulation at pH 5.2 (the pH of the Humira® formulation). The Gokarn Provisional teaches that high concentration antibodies can be prepared in "bufferless" liquid formulations. Ex. 1204, 1:1-8. The Gokarn Provisional includes data demonstrating that, at a concentration of 50 mg/mL, an exemplary IgG antibody has sufficient buffer capacity to control the pH for a liquid formulation in the pH range of 5.0-5.5. *Id.* at 9, 13. Moreover, the Gokarn Provisional explains that because all antibodies within a given class (e.g., all IgG antibodies) have similar amino acid sequences, ***all*** antibodies within a class will have similar buffering capacity at a given concentration. Ex. 1204, 3:1-15. A POSA therefore would have understood from the Gokarn Provisional that the IgG antibody in Humira® (i.e., 50 mg/mL adalimumab) possesses sufficient buffering capacity to maintain the formulation at a pH of 5.2.

The challenged claims also would have been obvious over Gokarn '011 in view of the 2003 Humira® Label. As the first therapeutic monoclonal antibody to be made commercially available in a high-concentration liquid formulation, 50

mg/mL adalimumab was the most prominent example of an antibody to be used in the "bufferless" formulations taught by Gokarn. Indeed, a POSA reading the Gokarn Provisional would have immediately recognized that the 50 mg/mL adalimumab, pH 5.2 formulation of Humira® could be converted to a "bufferless" formulation, and would have very reasonably expected to succeed in eliminating the citrate-phosphate buffer system.

Coherus has established, at a minimum, a reasonable likelihood that it would prevail with respect to at least one claim of the '619 patent. Indeed, all challenged claims are unpatentable as 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 recently 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 unpatentable as 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. This petition is substantively the same as, and intended to replace, the petition filed in IPR2017-0826.

Second, Coherus has filed a petition (IPR2017-00822) demonstrating that the challenged claims are anticipated by the Gokarn PCT under 35 U.S.C. §§ 102(a) and (e). The Gokarn PCT—as published on December 28, 2006 and as filed on June 8, 2006—discloses every element of the challenged claims and renders them unpatentable as anticipated or, alternatively, as obvious in view of the 2003 Humira® Label.

Third, Coherus has filed a petition (IPR2017-00823) 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 concurrently filed a petition demonstrating that the challenged claims are unpatentable as obvious over the 2003 Humira® Label in view of Fransson and buffer-free immunoglobulin products (essentially, IgG

antibodies and predominantly IgG1 antibodies), as described in the Gamimune® Label. That petition is substantively the same as, and intended to replace, the petition filed in IPR2017-0827.

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

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

Additionally, pursuant to the Patent Office Trial Practice Guide, 77 Fed. Reg. 48,756, 48,760 (Aug. 14, 2012), Coherus identifies out of an abundance of caution the following proceeding involving a patent claiming a common priority application with the '619 patent: U.S. Patent No. 8,420,081, which issued from U.S. Application Ser. No. 12/325,049 (to which the '619 patent claims priority), is

the subject of U.S. Patent Interference No. 106,057 (PTAB Declared May 18, 2016).

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

Coherus provides the following designation of counsel:

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

Please address all correspondence and service to counsel at the address provided in Section II.C. Coherus consents to electronic service at 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 of the '619 patent on the grounds listed in the table below. The '619 patent is to be reviewed under pre-AIA law.

Ground	Claims	Description	102(e) Date
1	16-19 and 24-30	Obviousness over the 2003 Humira® Label in view of Fransson and Gokarn '011	June 14, 2005
2	16-19 and 24-30	Obviousness over Gokarn '011 in view of the 2003 Humira® Label	June 14, 2005

The 2003 Humira® Label and Fransson were each published in recognized periodicals and readily accessible to the public and POSAs more than one year before November 30, 2007 (the earliest claimed priority date of the '619 patent) and are prior art under § 102(b). Ex. 1202 ¶¶ 68, 74. As established in Section IX, Gokarn '011 is prior art under § 102(e) as of June 14, 2005, the filing date of the

Gokarn Provisional. This Petition is accompanied by the declarations of Klaus-Peter Radtke, Ph.D. (Ex. 1202) and David Sherry, M.D. (Ex. 1207), 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. 1201, 152:16-39 (claims 16-18); Ex. 1202 ¶¶ 58-59. Adalimumab, also known as D2E7, has been recognized for nearly two decades as an antibody with promising therapeutic activity. Ex. 1202 ¶ 27. Adalimumab is the active agent in Humira®. *Id.* ¶ 28. Humira® was FDA approved for treatment of rheumatoid arthritis on December 31, 2002, and was commercially available in the United States beginning in early 2003. Ex. 1205, 471; Ex. 1209, 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. 1202 ¶¶ 29-30; Ex. 1205, 470; Ex. 1206, 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. 1202 ¶ 29; Ex. 1205, 470; Ex. 1206, 13.

Injection site pain was a known problem with Humira®. Ex. 1207 ¶¶ 21-22, 28-29; Ex. 1202 ¶¶ 70, 100-101. The 2003 Humira® Label 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. 1205, 472 (Table 4); Ex. 1207 ¶ 28; Ex. 1210 ¶¶ 117, 120; Ex. 1202 ¶¶ 70-73. 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. 1207 ¶¶ 28-29; Ex. 1210 ¶ 120; Ex. 1202 ¶ 102.

Adalimumab is a human IgG1 antibody. Ex. 1205, 470. All IgG antibodies have the same characteristic Y-shaped three-dimensional structure, and share highly homologous amino acid sequences. Ex. 1202 ¶¶ 33-35, 113-114; Ex. 1211, 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. 1202 ¶¶ 35-37; Ex. 1213, 111 ("Human IgG subclass proteins exhibit more than 95% primary amino acid sequence homology in their Fc regions…."); Ex. 1288, 20 ("[I]t is immediately apparent that the constant domains [of human IgG antibodies] have very similar sequences indeed – on average two subclasses show greater than 95% identity."); Ex. 1212, 178. Antibody sequences within each

subclass (e.g., IgG1) share an even higher degree of identity. Ex. 1202 ¶ 35. 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. *Id.* ¶ 36; Ex. 1211, 96-97, 102-03, Fig. 7-4.

A "humanized" antibody is one in which the CDRs from a non-human (e.g., mouse) antibody are grafted into a human antibody sequence. Ex. 1202 ¶ 37; Ex. 1214, 76. The overall sequence homology between a humanized IgG1 antibody and a human IgG1 antibody is therefore essentially the same as that found among fully human IgG1 antibodies. Ex. 1202 ¶ 37.

B. Buffer Systems

Independent claim 16 of the '619 patent covers *any* formulation of adalimumab in water without a "buffering system." Ex. 1201, 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. 1202 ¶ 41; Ex. 1215, 34; Ex. 1204, 6.

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. 1202 ¶ 41; Ex. 1215, 34; Ex. 1204, 6. This ability to resist pH change comes from certain compounds in solution that have dissociable protons (e.g., weak acids and bases). Ex. 1216, 526; Ex. 1202 ¶ 41. The dissociation constant of an acid (its "pK_a

value") is a measure of the strength of an acid in solution. Ex. 1202 ¶ 41. The most efficient buffers for a given solution contain compounds that have one or more dissociable protons with a pK_a value near that of the formulation's selected pH. *Id.*; Ex. 1216, 527 (indicating that buffers are "most efficient" when pH = pK_a); Ex. 1217, 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. 1203 ¶ 9; Ex. 1217, 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. 1202 ¶ 42 (citing Ex. 1217, 299; Ex. 1218, 597; Ex. 1272, 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. 1202 ¶¶ 42-44; Ex. 1219, 1012 ("The purpose of buffers in pharmaceutical formulations is to maintain a stable pH, usually that at which the drug is most stable."); Ex. 1217, 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. 1202 ¶¶ 56, 77, 106; Ex. 1219, 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. 1202 ¶¶ 53, 101-102; Ex. 1207 ¶¶ 32-34; Ex. 1220, ¶ 50 ("Citrate and phosphate buffers are much less preferred because [they cause] a painful reaction when injected subcutaneously."); Ex. 1219, 1012 (reporting reduction in pain with lower concentration of phosphate buffer). It was particularly well known that citrate causes pain on injection. Ex. 1219, 1012 ("citrate buffer causes pain"); Ex. 1217, 297 ("[C]itrate is known to cause stinging upon injection."); Ex. 1221, 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. 1207 ¶¶ 23-32; Ex. 1221, 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. 1222, 553 ("[L]ocal pain at the injection site is a common adverse event, 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. 1215; Ex. 1216, 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. 1215, 34; Ex. 1223, 715. The amino acids that contribute most to buffering capacity are those with dissociable protons 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. 1202 ¶ 42; s*ee* Ex. 1215, 34, 36. In 1967, Nozaki and Tanford published the pK_as of the dissociable protons for various amino acids in peptide chains. Ex. 1202 ¶¶ 42, 112; Ex. 1223, 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. 1202 ¶ 42; Ex. 1223, 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. 1202 ¶¶ 43-44, 113-116; *see also* Ex. 1224, 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. 1223, 715; Ex. 1215, 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. 1216, 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. 1202 ¶ 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.*; Ex. 1217, 307–31 (list of FDA-approved protein formulations). A POSA would not have expected those proteins to provide sufficient buffer capacity to be the *sole* source of pH control for such formulations. Ex. 1202 ¶ 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 were formulated at high protein concentrations and without a separate buffering system. *Id.* ¶¶ 46-47; Ex. 1218, 595-97. Many such immunoglobulin products are used to treat patients with immunodeficiency by providing a complete array of functional IgG antibodies. Ex. 1202 ¶¶ 46-48; Ex. 1225, 925 ("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. 1202 ¶¶ 46-48. 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.* ¶ 48; *see, e.g.*, Ex. 1226, 14–15 (BayTet® product: enriched in anti-tetanus antibody, to treat tetanus exposure). Notably, a series of such products, enriched in antibodies to different antigens, can all employ the same concentration, formulation pH, and excipients. Ex. 1202 ¶ 48 (citing BayHep®, BayRab®, BayRho®, and BayTet® products).

An example of one such immunoglobulin product is Gamimune®. Ex. 1225. 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. 1202 ¶¶ 49-52; Ex. 1225, 925. About 98% of the protein in Gamimune® was

IgG antibodies. Ex. 1202 ¶ 49; Ex. 1225, 925. The remaining protein was mostly serum albumin, along with trace amounts of IgA and IgM antibodies. *Id.* "The distribution of IgG subclasses is similar to that found in normal serum," (Ex. 1225, 925), meaning that about 65% of the IgG is of the IgG1 subclass, Ex. 1211, 101; Ex. 1202 ¶ 50. The Gamimune® label reports that "the buffer capacity of Gamimune N, 5% is 16.5 mEq/L (~ 0.33mEq/g protein)," demonstrating that POSAs understood that the concentrated protein itself provides the buffering capacity of the formulation. Ex. 1225, 925; Ex. 1202 ¶ 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. 1201, 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. 1202 ¶¶ 60-62; *see, e.g.*, Ex. 1201, 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. 1201, 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)."), 45:39-42.

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

To prepare the compositions of the alleged invention, a first formulation of protein, which contains excipients, is diafiltered using water so that the

concentration of excipients is greatly reduced. *Id.* at 3:37-42. In Example 1, for instance, an adalimumab formulation containing citrate-phosphate buffers, sodium chloride, and mannitol is diafiltered using a five-fold volume exchange with water to remove the excipients. *Id.* at 40:45-41:11. Theoretically, this filtration approach could have removed no more than 96.875% of the excipients. *Id.* at 43:48–60. Had the applicants used "constant volume diafiltration," the *theoretical* reduction in excipients would have increased to 99.3%. *Id.* The specification acknowledges that it would have been impossible to remove all excipients by the techniques described in the '619 patent. *See id.* at 10:61–63 ("[T]he total elimination of small molecules cannot be achieved in an absolute sense by DF/UF processing . . . .").

While the claims and certain examples of the '619 patent focus on anti-TNF alpha antibodies (and in some cases adalimumab, specifically), the '619 specification recognizes that a wide-range of proteins (including antibodies) can be prepared in an excipient-free formulation. *See, e.g.*, Ex. 1201, 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. 1202 ¶ 60.

B. The Prosecution History

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

a list of nearly 300 references submitted to the Patent Office by AbbVie, but they were never addressed by the Examiner during prosecution. *See* Ex. 1227, 208, 212; *see also* Ex. 1201, References Cited.

AbbVie first presented the challenged claims in a preliminary amendment filed November 21, 2014 in the '576 application. Ex. 1227, 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. 1228, 202–04, 271–73, 950–54, 1038–42; Ex. 1229, 4–14, 261–269, 1695–1704, 1735–49, 1868–88, 1946–69; Ex. 1230, 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). This person also would have had at least two years of experience preparing formulations of proteins suitable for therapeutic use. Ex. 1202 ¶ 64.

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. 1202 ¶¶ 66-67. 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. *Id.*; *see, e.g.*, Ex. 1201, 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. 1201, 10:61–63 ("[T]he total elimination of small molecules cannot be achieved in an absolute sense by DF/UF processing . . . ."); Ex. 1202 ¶ 67 (explaining that protein-solute interactions limit the ability to remove buffer components); Ex. 1231, 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. 1202 ¶ 67.

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

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

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

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

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

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

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

A. The Gokarn Provisional (Ex. 1204) Satisfies the Requirements of Pre-AIA 35 U.S.C. § 112, ¶1 for at least Claims 162 and 165 of Gokarn '011.

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

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

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

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

Ex. 1203, 37; Ex. 1204, 14.

[2] The Gokarn Provisional appears to have been drafted to obtain a filing date on work that was about to be publicly presented, inasmuch as it contains only a single claim and the majority of its disclosure appears to be a PowerPoint presentation. *See* Ex. 1204, 4-14.

While the Gokarn Provisional is directed to a method of preparing formulations and claim 162 of Gokarn '011 is directed to the formulation itself, a POSA would have understood that the Gokarn Provisional also describes buffer-free antibody formulations, as discussed below. Ex. 1202 ¶¶ 90-91. The other minor difference is that claim 162 expressly states "wherein the formulation lacks a buffer, apart from the antibody."

A POSA would have understood that the Gokarn Provisional discloses formulations wherein the formulation lacks a buffer, apart from the antibody. *Id.* ¶¶ 82-89, 91, 94, 110. The title of the Gokarn Provisional is "***Bufferless*** Protein Formulation." Ex. 1204, 1 (Title) (emphasis added). The Gokarn Provisional further discloses a preferred embodiment in which "the pharmaceutically active compound is the buffering agent," *id.* at 1:15-17, and teaches that "there will be a crossover concentration, wherein the antibody formulation ***will not require the addition of an extraneous buffer*** (like acetate) to maintain pH," *id.* at 3:6-13 (emphasis added).

Moreover, the Gokarn Provisional includes actual data measuring the buffering capacity of "EMAB" (epratuzumab) formulations without an extraneous buffer. *Id.* at 8-10; Ex. 1202 ¶¶ 84-88, 92, 110, 138. A POSA would readily conclude from the disclosure of the Gokarn Provisional that Gokarn was in

possession of antibody formulations without a buffer "apart from the antibody," as claimed in claim 162 of the Gokarn '011 application. Ex. 1202 ¶¶ 90-92.

The Gokarn Provisional also enables Gokarn '011 claim 162. As an initial matter, the Gokarn Provisional is presumed enabling for all it teaches. *In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012) ("[A] prior art printed publication cited by an examiner is presumptively enabling barring any showing to the contrary by a patent applicant or patentee."); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003) (holding presumption of enablement applies in district court proceedings as well as during prosecution). Moreover, the Gokarn Provisional teaches a POSA how to make and use the subject matter within the scope of Gokarn '011 claim 162. For example, the Gokarn Provisional discloses diafiltration methods for exchanging the solvent system for EMAB formulations, Ex. 1204, 4-5, and demonstrates that the inventors had already made "bufferless high concentration EMAB solutions," *id.* at 13 (describing studies as "on-going"), *see also id.* at 8-9 (measuring buffer capacity of "EMAB alone"). Post-invention testing (such as that disclosed in Gokarn '011) also demonstrates that the Gokarn Provisional's diafiltration methods are useful to prepare buffer-free formulations of a variety of pharmaceutical antibodies. Ex. 1203 ¶¶ 379, 388, 392; *see In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (finding post-invention testing relevant "to prove that the disclosure was in fact

enabling when filed"); *see also Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987). Finally, AbbVie has admitted to the Board that, by June 2005, removing buffer from a protein solution was enabled. Ex. 1232, 4 (citing Ex. 1233; Ex. 1234) (stating that a POSA "would have readily known that routine techniques . . . such as dialysis or size exclusion chromatography[] could be used to remove the buffer from a protein solution.").

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

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

Claim 165 of Gokarn '011 reads:

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

Ex. 1203, 37. This claim is also described and enabled by the Gokarn Provisional. Ex. 1202 ¶¶ 94-95. The Gokarn Provisional demonstrates that Gokarn possessed buffer-free formulations of "Emab(AMG412) " or "EMAB." Ex. 1204, 4-5, 8-10, 13. Both "Emab" and "AMG412" were widely known at the time to refer to epratuzumab. Ex. 1202 ¶¶ 85-86; Ex. 1235; Ex. 1236, 3986s, Figure 4; Ex. 1237, 1. Claim 165 is enabled by the Gokarn Provisional for the same reasons stated above for claim 162. Therefore, the Gokarn Provisional sufficiently discloses claim 165 of Gokarn '011 as required by § 119(e).

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

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

There are four applications in the chain leading back from Gokarn '011 to the Gokarn Provisional: U.S. Application No. 13/797,622; U.S. Application No. 13/188,329; U.S. Application No. 11/917,188; and PCT/US2006/022599 (collectively, the "Intermediate Applications"). Gokarn '011 and each of the Intermediate Applications properly claim priority to the Gokarn Provisional, without a break in the priority chain. Ex. 1203 ¶ 1; Ex. 1238 ¶ 1; Ex. 1239 ¶ 1; Ex. 1240 ¶ 1; Ex. 1241, 1:3-5. Moreover, for the reasons below, each of these applications discloses claims 162 and 165 of Gokarn '011.

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

An application may incorporate a provisional application by reference. *Trs. of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1365-66 (Fed. Cir. 2016). In such cases the "provisional applications incorporated by reference are 'effectively part of the' specification as though [they were] 'explicitly contained therein.'" *Id.*

(quoting *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000)).

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

Each of the Intermediate Applications and Gokarn '011 incorporate the Gokarn Provisional by reference, using the same unequivocal language: "This application … claims full priority benefit of U.S. Provisional Application Ser. No. 60/690,582 filed 14 Jun. 2005, which is incorporated herein by reference in its entirety." Ex. 1203 ¶ 1; Ex. 1238 ¶ 1; Ex. 1239 ¶ 1; Ex. 1240 ¶ 1; Ex. 1241, 1:3-5. This language is sufficient to incorporate the entire disclosure of the Gokarn Provisional. *See, e.g.*, *Harari*, 656 F.3d at 1335.

As explained in Section IX.A. above, the Gokarn Provisional supports at least claims 162 and 165 of Gokarn '011, and its incorporation by reference into the Intermediate Applications and Gokarn '011 renders claims 162 and 165

supported by all applications in the priority chain. Additionally, the disclosure of the Gokarn Provisional is carried forward into each of Gokarn'011 and the Intermediate Applications, as described below.

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

Independent of their incorporation by reference of the Gokarn Provisional, Gokarn '011 and the Intermediate Applications (which include substantially the same specification as Gokarn '011) satisfy the written description and enablement requirements of 35 U.S.C. § 112, ¶1 with respect to claims 162 and 165. Ex. 1202 ¶¶ 90-96; Ex. 1203; Ex. 1238; Ex. 1239; Ex. 1240; Ex. 1241.

For example, the references' specifications disclose "pharmaceutically acceptable formulations comprising a pharmaceutical protein, that are buffered by the protein itself, that do not require additional buffering agents to maintain a desired pH, and in which the protein is substantially the only buffering agent." Ex. 1203 ¶ 11; Ex. 1238 ¶ 11; Ex. 1239 ¶ 11; Ex. 1240 ¶ 11; Ex. 1241, 3:17-20. They further explain that "'[s]elf-buffering' means the capacity of a substance, such a pharmaceutical protein, to resist change in pH sufficient for a given application, in the absence of other buffers." Ex. 1203 ¶ 141. They describe various pharmaceutical excipients that may be included. *Id.* ¶ 308. With respect to claim 165, the specification specifically refers to epratuzumab. *Id.* ¶ 263.

Gokarn '011 also enables claims 162 and 165. As with the Gokarn Provisional, it is presumed enabling for all that it teaches. *In re Antor*, 689 F.3d at 1288; *Amgen, Inc.*, 314 F.3d at 1355. Moreover, Gokarn '011 discloses the same diafiltration methods for preparing the self-buffering antibody formulations that are disclosed in the Gokarn Provisional and the '619 patent. Ex. 1203 ¶ 357-59. Moreover, as explained in Section IX.A.1. above, AbbVie has previously informed the Board that such processes were enabled before June 2005. Ex. 1232, 4 (citing Ex. 1233, Ex. 1234).

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

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

Petitioner's obviousness analysis appears in Section X below. As Section X makes clear, the subject matter on which Petitioner relies is disclosed in the Gokarn Provisional. That subject matter is also disclosed in Gokarn '011 and in the Intermediate Applications, both through the incorporation of the Gokarn Provisional (*see* Section IX.B.1. *supra*) and independently (*see* Ex. 1202, App'x D (citing Gokarn '011 specification)). In view of the foregoing, Gokarn '011 is

available as prior art under 35 U.S.C. § 102(e) as of the June 14, 2005 filing date of the Gokarn Provisional.

X. THE CHALLENGED CLAIMS ARE UNPATENTABLE AS OBVIOUS OVER THE 2003 HUMIRA® LABEL IN VIEW OF FRANSSON AND GOKARN '011 (GROUND 1)

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 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); *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

For purposes of obviousness, the disclosure of the Gokarn Provisional, which is carried forward into Gokarn '011, is prior art as of June 14, 2005. *See 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….").

A. Claims 16-18 Are Obvious Over the 2003 Humira® Label in View of Fransson and Gokarn '011

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. 1201, 152:15-33; Ex. 1202 ¶ 97; *Compare* Ex. 1201, SEQ ID Nos. 3-8, *with* Ex. 1242, 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. 1201, 152:34-37; Ex. 1202 ¶¶ 127-128; *Compare* Ex. 1201, SEQ ID Nos. 1-2, *with* Ex. 1242, SEQ ID Nos. 1-2. Claim 18 depends from claim 17 and requires "wherein the antibody is adalimumab." Ex. 1201, 152:38-39. Thus, the antibody required by each of claims 16-18 is satisfied by a disclosure of adalimumab. *See* § 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. 1202 ¶ 98; Ex. 1205, 470 ("Each 0.8 mL HUMIRA contains 40 mg adalimumab … and Water for Injection ….") The 2003 Humira® Label discloses that the formulation contains a citrate-

phosphate buffer. Ex. 1202 ¶¶ 68-69, 98; Ex. 1205, 470. 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 expected 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, and a POSA would have recognized that the buffer system was the most likely cause of that pain. Ex. 1202 ¶¶ 70-72, 99-103; Ex. 1207 ¶¶ 32-35. Removing the buffer altogether—as taught by Gokarn '011—carried the additional advantage of eliminating unnecessary excipients from the formulation. Ex. 1202 ¶¶ 54, 103-105.

The Gokarn Provisional taught that liquid formulations with high antibody concentrations (e.g., 50 mg/mL) could be "bufferless," because "antibodies at

sufficiently high concentrations, possess adequate buffering capacity in the pH range of 4.0 to 6.0, to provide pH control for a liquid formulation." Ex. 1204, 1:5-8. The fact that applying the teachings of Gokarn '011 to the FDA-approved 50 mg/mL adalimumab Humira® formulation led to the expected result (i.e. a pH-stable buffer-free formulation having 50 mg/mL of adalimumab) indicates that the claimed invention is only the product of ordinary skill and common sense—not innovation. *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. Ex. 1202 ¶¶ 100-102. A POSA would have understood that the most likely source of that pain was the citrate-phosphate buffer. *Id.*

The Humira® Label itself discloses, in Table 4, that 12% of patients reported injection site pain as an adverse event during clinical trials. *Id.* ¶¶ 70, 100; Ex. 1205, 472. 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. 1207 ¶ 28. The label also states that 12% of patients receiving placebo in Humira® clinical trials reported injection site pain. Ex. 1205, 472. 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 X.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. 1202 ¶¶ 70-72, 100; Ex. 1207 ¶ 28; Ex. 1210 ¶ 120 (describing same 636-patient clinical trial 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. 1207 ¶ 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.* ¶¶ 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. 1271, 5. Injection site pain also was recognized as a "major side effect" of Humira® in the literature. Ex.

1243, 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. 1207 ¶ 23; *see, e.g.*, Ex. 1244, S19 (stating that whether patients take the drug as directed is "possibly the most important factor in maintaining the benefits of anti-TNF therapy"); Ex. 1221, 218 ("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. 1202 ¶¶ 53, 100-102; Ex. 1207 ¶ 32; Ex. 1219, 1012 ("citrate buffer causes pain"); Ex. 1221, 218 (teaching that citrate buffer causes significantly more pain on injection than histidine and saline); Ex. 1217, 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. 1222, 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. 1220 ¶ 50 ("Citrate and phosphate buffers are much less preferred because [they cause] a painful reaction when injected subcutaneously."); *see* Ex. 1219, 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. 1219, 1012. 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. 1202 ¶ 106. 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. 1202 ¶¶ 76-77, 106-108.

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. *Id.* ¶¶ 101-102. To the contrary, polysorbates such as the polysorbate 80 excipient in Humira® had been linked with a ***reduction*** in pain on injection. *Id.*; Ex. 1245, 297. Therefore, a POSA would have known that Humira®'s citrate-phosphate buffer system was the most likely cause of the pain on injection. As a result, a POSA would have been motivated to eliminate the citrate-phosphate buffer system. Ex. 1202 ¶¶ 100-103.

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. Between these two choices, the POSA had many good reasons to eliminate the extrinsic buffer altogether, as discussed further below. *Id.* ¶¶ 103-108.

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. 1202 ¶ 104. 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. 1217, 294-95 (emphasis added); *see also* Ex. 1270, 2 (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. 1202 ¶¶ 54, 104; *see also* Ex. 1246, 2 ("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. 1217, 297 (discussing deleterious interactions with various buffer systems).

As the Gokarn Provisional taught, when the protein concentration is high enough to provide sufficient buffering capacity to maintain the formulation pH, an

extraneous buffering system is unnecessary. Ex. 1204, 1:5-8 ("[A]ntibodies at sufficiently high concentrations, possess adequate buffering capacity in the pH range of 4.0 to 6.0, to provide pH control for a liquid formulation."). A POSA would have understood from the Gokarn Provisional that adalimumab at 50 mg/mL would possess sufficient buffering capacity to "obviate the need for a separate buffering agent," and therefore would have eliminated Humira®'s citrate-phosphate buffer. Ex. 1204, 2:22-23; *see* Section X.A.4 *infra*.

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. 1202 ¶¶ 54-55, 105. 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 Gokarn '011

A POSA would have expected success in eliminating the citrate-phosphate buffering system from Humira® based on the teachings of the Gokarn Provisional, which are carried forward into Gokarn '011. *Id.* ¶¶ 109-120. A POSA would have understood from the Gokarn Provisional that, at least for antibodies in the IgG class (such as adalimumab), approximately 50 mg/mL of antibody "possess[es] adequate buffering capacity in the pH range of 4.0 to 6.0, to provide pH control for a liquid formulation." Ex. 1204, 1:5–8; Ex. 1202 ¶¶ 109-116.

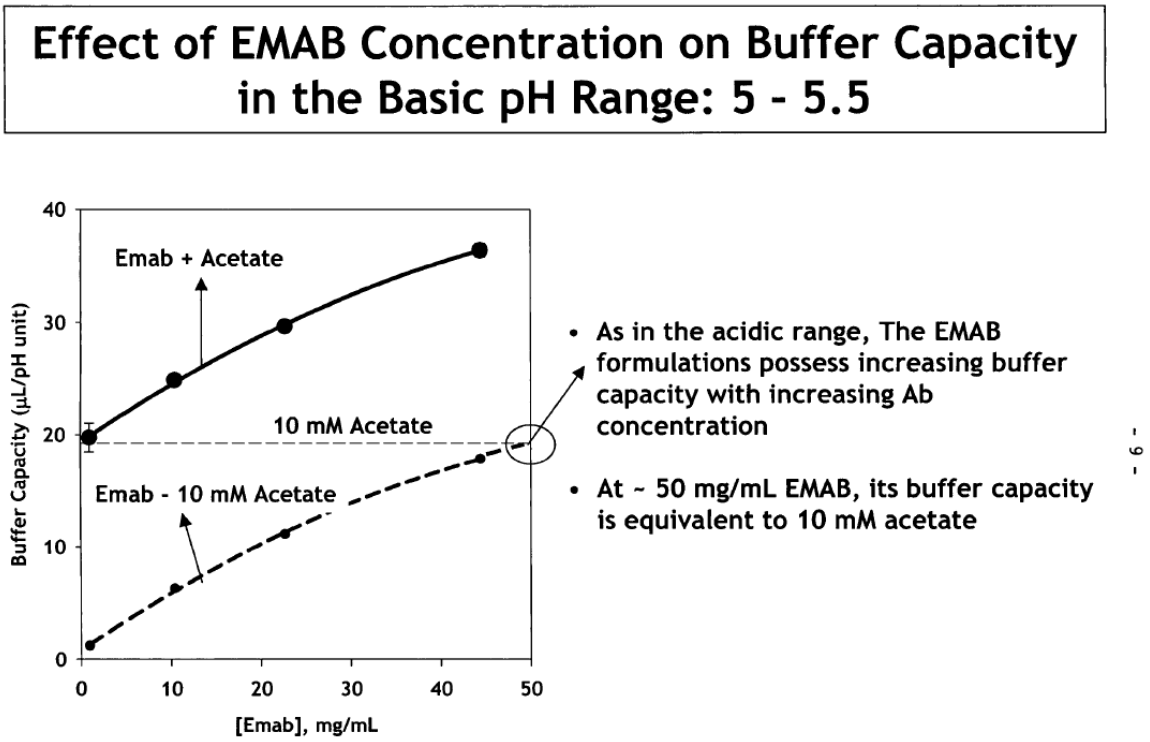
The Gokarn Provisional teaches that pharmaceutical antibodies in general, when formulated at high enough concentrations, have sufficient buffering capacity to be formulated without extraneous buffers. Ex. 1202 ¶¶ 109-110; Ex. 1204, 1:5–17. It also taught that the buffer capacity of an antibody is derived from the ionizable groups of its constituent amino acids—particularly glutamic acid, aspartic acid, and histidine residues for formulations in the pH range of 4 to 6. Ex. 1204, 2:18–31; Ex. 1202 ¶¶ 41, 113 (explaining that amino acids are only effective buffers within about 1 pH unit of their pK_a and only Glu, Asp, and His, have a pK_a within about 1 pH unit of 5.2). Therefore, "it is not the function or necessarily the structure of the protein that is determinative" of its buffer capacity; rather it is the antibody's amino acid composition that determines buffer capacity. Ex. 1204,

2:15–23; Ex. 1202 ¶¶ 81-84, 110-113. A POSA thus would have expected antibodies with similar amino acid compositions to have similar buffer capacity. Ex. 1202 ¶¶ 111-113,125.

The Gokarn Provisional expressly points out that the number of amino acids contributing ionizable groups is "relatively constant for a given class of monoclonal antibodies" and therefore buffering capacity will be similar among ***all*** antibodies of the same class (e.g., IgG antibodies). Ex. 1204, 3:1-10; Ex. 1202 ¶¶ 113, 125. Moreover, POSAs knew that amino acid sequences for antibodies within a given class (e.g., IgG) share a high degree of identity, particularly for antibodies in the same subclass (e.g., IgG1 or IgG2). Ex. 1202 ¶¶ 33-37, 113-115; Ex. 1213, 111 ("Human IgG subclass proteins exhibit more than 95% primary amino acid sequence homology in their Fc regions….").

The Gokarn Provisional provides data demonstrating the buffer capacity for an exemplary antibody, "Emab (AMG412)," which a POSA would have recognized as the humanized IgG1 antibody epratuzumab. Ex. 1204, 5, 9; Ex. 1202 ¶¶ 85-86 (citing prior art publications Ex. 1235, Ex. 1236, and Ex. 1237, demonstrating that a POSA would have understood the Gokarn Provisional's references to EMAB and AMG412 to unambiguously refer to epratuzumab). The data show that epratuzumab displays significant buffering capacity in the pH range of 5.0 to 5.5 that increases almost linearly with concentration. Ex. 1202 ¶¶ 88,

110, 116 (discussing Ex. 1204, 9). The Gokarn Provisional's graph below illustrates that a buffer-free formulation containing 50 mg/mL of "EMAB" (an IgG1 antibody) would have the same buffer capacity as 10 mM acetate (a common commercial buffer) in the pH range 5–5.5. Ex. 1204, 9; Ex. 1202 ¶¶ 88, 110; Ex. 1217, 299 (referring to acetate as "the most commonly used buffer in the acidic pH range of 4.0 to 5.5").



Ex. 1204, 9.

Gokarn uses the buffering capacity of 10 mM acetate as a "benchmark" for sufficient buffering capacity to avoid the need for "addition of an extraneous buffer." Ex. 1202 ¶ 110; Ex. 1204, 3:10-13. Specifically, the Gokarn Provisional states that for antibodies in general, "there will be a *crossover concentration*,

wherein the antibody formulation will not require the addition of an extraneous buffer (like acetate) to maintain pH." Ex. 1204, 3:10-13 (emphasis added). Based on the data above, the Gokarn Provisional determines that "[t]he *crossover concentrations* of EMAB (to be comparable to 10 mM acetate) are ~30 mg/mL in the pH 4.5-5.0 range, ~50 mg/mL in the pH 5.0-5.5 range." *Id.* at 13 (emphasis added). Accordingly, a POSA would have understood from the Gokarn Provisional that about 50 mg/mL of an IgG antibody would possess sufficient buffering capacity in the pH range of 5-5.5 such that it would "not require the addition of an extraneous buffer." Ex. 1204, 3:10-13; Ex. 1202 ¶¶ 88, 110-116.

A POSA would have understood that the Gokarn Provisional's demonstration of buffering capacity for EMAB also would apply to adalimumab (and to IgG antibodies in general). Ex. 1202 ¶¶ 109-118. The POSA would have known that the amino acid sequences and tertiary structure of epratuzumab and adalimumab are highly similar because both antibodies share the constant regions of a human IgG1 antibody. *Id.* ¶¶ 37, 114; Ex. 1214, 76; Ex. 1213, 111.

Adalimumab, epratuzumab, and other IgG1 antibodies therefore all have highly similar numbers of aspartic acid (Asp), glutamic acid (Glu), and histidine (His) residues. Ex. 1202 ¶¶ 42, 81-83, 114. The Gokarn Provisional teaches that these three amino acids are the critical residues that contribute to buffer capacity around pH 5.2. *Id.* ¶¶ 81-83, 111-115; Ex. 1204, 2:27-31. Moreover, the Gokarn

Provisional's disclosure of protein buffer capacity was not a new concept; papers from the 1960s identified the same amino acids as contributing to a protein's buffer capacity in the pH range around 5.2. Ex. 1202 ¶¶ 42-44, 112; Ex. 1215, 34; Ex. 1223, 721 (publishing pK_as of amino acids in proteins). Because the amino acid residues are responsible for an antibody's ability to provide pH control in the 4-6 pH range, a POSA would have expected that, as the Gokarn Provisional taught, IgG antibodies all would have very similar buffer capacities at a given concentration. Ex. 1202 ¶¶ 113-115. A POSA therefore would have expected that 50 mg/mL of adalimumab, like 50 mg/mL of EMAB, had sufficient buffer capacity to be the sole source of pH control for an aqueous pharmaceutical formulation. *Id.* ¶¶ 113-116.

Of course, the challenged claims are not limited only to 50 mg/mL; they include concentrations up to four times greater (200 mg/mL). Because a protein's buffer capacity increases almost linearly with concentration, a POSA would have been confident that these concentrations would have also provided sufficient buffer capacity to be an aqueous formulation's sole source of buffer capacity near pH 5.2. *Id.* ¶¶ 43-44, 115-118, 151; Ex. 1204, 8-9 (showing increasing capacity with increased concentration).

Notably, the fact that the FDA-approved formulation of adalimumab included a buffer system would not have detracted from a POSA's expectation of

success in removing it. Ex. 1202 ¶ 108. The initial formulation of a therapeutic often is established relatively early during development, because of the necessity for long-term stability studies. *Id.* 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. 1247, 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. 1202 ¶ 108. However, after the launch of Humira® at 50 mg/mL, a POSA would have reasonably expected success in formulating it without a separate buffer, especially in view of the Gokarn Provisional's demonstration that 50 mg/mL of an IgG1 antibody provides as much buffering capacity as a traditional buffering system. *Id.* ¶¶ 108-116.

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 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. *Id.* ¶¶ 118-120; *see* Ex. 1204, 1:5-8 (stating

that the high-concentration antibody "provide[s] pH control for a liquid formulation").

POSAs recognized that formulating a protein at the optimal pH is an important consideration for preparing a stable formulation. Ex. 1202 ¶¶ 118-119; *see, e.g.* Ex. 1217, 297 ("The stability of a protein is usually observed to be maximal in a narrow pH range."), 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. 1202 ¶¶ 38, 118; Ex. 1217, 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. 1202 ¶ 119; *see* Ex. 1205, 470. A POSA would have expected success in using the high-concentration antibody to maintain the formulation at a pH of 5.2, and the antibody was known to be stable at that pH. Ex. 1202 ¶¶ 118-120, 122. Indeed, eliminating the extraneous buffer system would have been expected to reduce the potential for certain chemical degradation reactions. *Id.* ¶ 120, 122; Ex. 1217, 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. 1202 ¶ 120; Ex. 1217, 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. 1202 ¶ 120; Ex. 1217, 293. Surfactants (e.g., polysorbate 80) are used to "inhibit surface-induced aggregation phenomena." Ex. 1202 ¶ 120; Ex. 1217, 293. The challenged claims do not exclude the presence of any of these stabilizer molecules. Ex. 1202 ¶ 120; *see* Ex. 1201, claims 16-19, 24-30.

A POSA also would have known how to make the buffer-free 50 mg/mL adalimumab formulation. The Gokarn Provisional taught use of standard diafiltration techniques to exchange the solvent in a protein formulation, thereby removing the buffer. Ex. 1202 ¶¶ 95, 117; Ex. 1204, 4-5. Moreover, AbbVie has previously urged 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. 1232, 4 (citing Ex. 1233; Ex. 1234).

5. The Board's Reasoning in Denying Coherus' Request for Rehearing in IPR2016-01018 is Not Applicable Here

Coherus filed IPR2016-01018 challenging AbbVie's U.S. Patent No. 9,114,166 ("the '166 patent"). The '166 patent claims priority to an application filed in 2002—more than ***five years before*** the effective filing date of the '619

patent. Ex. 1287, 1. The state of the art applicable to the '166 patent was, therefore, very different from that existing as of the '619 patent's effective filing date. The '166 patent claimed a "stable liquid aqueous pharmaceutical formulation" comprising 50 mg/ml adalimumab and a buffer. *Id.* at claim 9. Here, years before the '619 patent's effective filing date, Humira® was commercially available and the 2003 Humira® Label taught an aqueous pharmaceutical formulation of adalimumab at 50 mg/ml, disclosing an appropriate pH and excipients for such a formulation. Ex. 1202 ¶¶ 121-124; Ex. 1205, 470.

In denying Coherus' request for rehearing on the '166 patent, the Board focused on the uncertainty in applying a formulation for one antibody to a different antibody. The Board relied primarily on Wang 2007 (Ex. 1286), emphasizing the statement that "'[d]evelopment of commercially viable antibody pharmaceuticals has … not been straightforward. This is because the behavior of antibodies seems to vary, *even though they have similar structures*.'" IPR2016-01018, Paper No. 12, 3 (quoting Ex. 1286, 5 (Board's emphasis)). A POSA would have considered Wang 2007 largely irrelevant here because, as of the critical date for the '619 patent, adalimumab had been successfully formulated as an aqueous, 50 mg/ml pharmaceutical composition. Ex. 1202 ¶¶ 121-124. ***The question here is not whether an aqueous pharmaceutical formulation of 50-200 mg/ml adalimumab***

could be made, but only whether there was a reasonable expectation of success in formulating it without a separate buffering system. *Id*.

The Gokarn Provisional expressly teaches that 50 mg/mL of an IgG antibody would provide sufficient pH control for a formulation in pH range of about 4 to 6, rendering a separate buffering system unnecessary. *Id.* ¶ 125; *see* Section X.A.4. Adalimumab is indisputably an IgG and, specifically, an IgG1 antibody. Ex. 1205, 470. The Gokarn Provisional discloses that the structural and sequence differences between different IgG antibodies do *not* lead to significant differences in buffer capacity. Ex. 1204, 3:6-10; Ex. 1202 ¶ 125. Gokarn taught that antibodies within a class all have similar buffer capacity, and demonstrated that an IgG1 antibody can self-buffer. Ex. 1202 ¶ 125.

The Gokarn Provisional's specific teaching that antibodies within the IgG class, and specifically the IgG1 subclass, had sufficient self-buffering capacity to be formulated without extraneous buffer compounds provided a POSA with *at least* a reasonable expectation of success in preparing aqueous, bufferless formulations of adalimumab at the concentrations claimed in the '619 patent. *Id.* "[G]eneral statements regarding the unpredictability associated with developing drug formulations" in the prior art—such as those in Wang 2007—would not have discouraged a POSA given the express, data-supported teachings in the Gokarn Provisional. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013).

As the Federal Circuit has held, "'obviousness cannot be avoided simply by showing some degree of unpredictability in the art so long as there was a reasonable probability of success.'" *Id.* (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007)).

In sum, 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 Gokarn '011. Ex. 1202 ¶¶ 97-126. 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. *Id.* ¶¶ 100-107. A POSA also would have been motivated to combine the Humira® formulation with Gokarn '011, because both references relate to pharmaceutical formulations for IgG antibodies at high concentrations. *Id.* ¶ 109. A POSA would have recognized that the bufferless antibody formulations taught by the Gokarn Provisional elegantly conform with Fransson's guidance to avoid citrate and reduce the buffering capacity of a formulation to reduce injection site pain. *Id.* ¶¶ 103-111; Ex. 1219, 1012.

B. Claim 19 of the '619 Patent Is Obvious Over the Humira® Label in view of Fransson and Gokarn '011

Claim 19 recites "[t]he formulation of claim 16, wherein the formulation further comprises a non-ionizable excipient." The Gokarn Provisional teaches that its bufferless formulations may include other desired ingredients, such as

"surfactants (e.g. polysorbate), polyols … salts and preservatives." Ex. 1204, 1:26-30. The FDA-approved Humira® formulation included such non-ionizable excipients. Ex. 1202 ¶ 129. Specifically, Humira® contains 9.6 mg mannitol and 0.8 mg polysorbate 80, both of which are non-ionizable excipients. *Id.*; Ex. 1205, 470.

It would have been obvious to a POSA that these other excipients could remain if so desired when removing the citrate-phosphate buffer system from Humira®. Ex. 1202 ¶¶ 120, 130. These other excipients would not have been expected to contribute to injection site pain. *Id.* Claim 19 of the '619 patent therefore would have been obvious over the Humira® Label in view of Gokarn '011.

C. Claims 24-30 of the '619 Patent Are Obvious Over the Humira® Label in view of Fransson and Gokarn '011

Claims 24 and 27 depend from claims 16 and 18, respectively, and require that "the pH of the formulation is from 4 to 8." Claims 25 and 28 depend from claims 16 and 18, respectively, and require that "the pH of the formulation is from 4 to 6." Claims 26 and 29 depend from claims 16 and 18, respectively, and require that "the pH of the formulation is from 5 to 6." Claim 30 depends from claim 18 and requires that the pH is 5.2. Ex. 1201, claims 24-30.

The 2003 Humira® Label taught that the product was formulated at a pH of 5.2. Ex. 1205, 470. 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. 1202 ¶ 134. Moreover, the Gokarn Provisional's disclosure that 50 mg/mL epratuzumab had sufficient buffering capacity in the pH range of 5.0 – 5.5 to obviate the need for a separate buffering system, would have led a POSA to reasonably expect that 50 mg/mL adalimumab would have sufficient buffering capacity to maintain a pH of 5.2 in a liquid formulation. *Id.* ¶¶ 109-116.

Because 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, those claims all are obvious over the 2003 Humira® Label in view of Fransson and Gokarn '011. *See In re Harris*, 409 F.3d 1339, 1341 (Fed. Cir. 2005) ("[A] prima facie case of obviousness arises when the ranges of a claimed composition overlap the ranges disclosed in the prior art.").

Additionally, the Gokarn Provisional teaches that "antibodies at sufficiently high concentrations, possess adequate buffering capacity in the pH range of 4.0 to 6.0, to provide pH control for a liquid formulation." Ex. 1204, 1:5-8. The Gokarn Provisional thus discloses the identical pH range of 4 to 6 claimed in claims 25 and 28. The Gokarn Provisional's range of "4.0 to 6.0" falls within the slightly broader pH of "from 4 to 8" of claims 24 and 27, and "completely encompasse[s]" both the range of "from 5 to 6" recited in claims 26 and 29 and the pH 5.2 of claim 30. *In re Harris*, 409 F.3d at 1341. The '619 patent gives no indication that any of the

claimed ranges are critical, and therefore the disclosure of the Gokarn Provisional, carried forward into Gokarn '011, renders obvious each of claims 24-30. *See id.*

XII. THE CHALLENGED CLAIMS ARE UNPATENTABLE AS OBVIOUS OVER GOKARN '011 IN VIEW OF THE HUMIRA® LABEL (GROUND 2)

A. Claims 16-18 of the '619 Patent Are Obvious over Gokarn '011 in view of the Humira® Label

The Gokarn Provisional teaches that IgG antibodies "at sufficiently high concentrations" can "provide pH control for a liquid formulation" without the need for traditional buffering agents. Ex. 1204, 1:5-8; *see also* Section X.A.4 *supra.* It teaches that, for an IgG1 antibody, a "sufficiently high concentration" is about 30-50 mg/mL in the pH range of 4.5-5.5, and specifically 50 mg/mL in the 5.0-5.5 pH range. Ex. 1204, 13; Ex. 1202 ¶¶ 136-138. The Gokarn Provisional teaches that at such high concentrations, a separate buffering agent is unnecessary and can be removed. Ex. 1202 ¶ 137; *see, e.g.*, Ex. 1204, 2:19-23 (stating that proteins at high enough concentration "obviate the need for a separate buffering agent"). Accordingly, the Gokarn Provisional expressly motivates a POSA to eliminate extraneous buffering systems from high-concentration antibody formulations. Ex. 1202 ¶¶ 137-139. Moreover, A POSA would have recognized that elimination of the extraneous buffering system was beneficial because it avoids unnecessary exposure to foreign substances for the patient, and reduces costs by simplifying regulatory and process controls. Ex. 1202 ¶¶ 54-55, 105; *see* Section X.A.3 *supra*.

A POSA reading the Gokarn Provisional's disclosure that 50 mg/mL or higher of EMAB (an IgG1 antibody) provided effective buffering in the pH 5.0 – 5.5 range, Ex. 1204, 9-10, would have immediately envisioned Humira® (50 mg/mL adalimumab, another IgG1 antibody, formulated at pH 5.2) as the prime example of an antibody "at sufficiently high concentration[]" to "provide pH control for a liquid formulation" without extraneous buffering agents, *id.* at 1:5-8. Ex. 1202 ¶ 138. The POSA would have been motivated to select adalimumab as the antibody for use in the "bufferless" formulations described by the Gokarn Provisional because it had already been commercialized in the high concentration (*i.e.*, 50 mg/mL) and pH ranges (*i.e.*, a pH of 5.2) disclosed by Gokarn. *Id.* ¶¶ 138-140; Ex. 1205, 470.

Prior to the priority date of the '619 patent, there were very few liquid pharmaceutical antibodies known to be formulated at concentrations around 30 mg/mL or higher. Ex. 1202 ¶ 138; Ex. 1217, 307–31 (list of FDA-approved protein formulations). Perhaps the most prominent antibody within that category was adalimumab. Ex. 1202 ¶ 138. Humira® was widely prescribed and well known in the pharmaceutical antibody field. Ex. 1209. And, as AbbVie has previously touted to the Board, adalimumab was the first liquid monoclonal antibody formulation to have been FDA-approved and commercialized at a high concentration. Ex. 1248, 12.

A POSA would have had a reasonable expectation of success in formulating adalimumab in a buffer-free aqueous formulation at 50 mg/mL for all the same reasons discussed in Section X.A.4 above. Ex. 1202 ¶¶ 109-120. That is, the POSA would have understood that 50 mg/mL adalimumab would have about the same buffering capacity as 50 mg/mL epratuzumab, because both are IgG1 antibodies and therefore share very similar amino acid sequences and tertiary structure. *Id.* ¶¶ 37, 114. Though not a claim requirement, a POSA would have expected the buffer-free formulation to be stable because it would maintain the same pH of 5.2 as the commercial formulation. *Id.* ¶¶ 118-125.

In sum, Humira® was a "piece of prior art ready for the improvement" disclosed by the Gokarn Provisional, which is carried forward into Gokarn '011. *KSR*, 550 U.S. at 417. The substitution of adalimumab (or other high-concentration IgG antibodies) for epratuzumab in a buffer-free formulation would have been obvious, particularly because Gokarn explicitly teaches that high concentration antibodies in general can be formulated without an extraneous buffer. Ex. 1204, 1:5-8; *KSR*, 550 U.S. at 417 ("[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").

B. Claim 19 of the '619 Patent Is Obvious Over Gokarn '011 in view of the 2003 Humira® Label

Claim 19 recites "[t]he formulation of claim 16, wherein the formulation further comprises a non-ionizable excipient." The Gokarn Provisional teaches that non-ionizable excipients, including "polysorbate," can be included in the bufferless formulation. Ex. 1204, 1:26-30. The 2003 Humira® Label also teaches the inclusion of non-ionizable excipients, including "polysorbate 80," in the 50 mg/mL adalimumab formulation. Ex. 1205, 470. A POSA could have included these non-ionic excipients in a buffer-free aqueous formulation of 50 mg/mL adalimumab with a reasonable expectation of success. Ex. 1202 ¶¶ 143-145. Claim 19 therefore is obvious over Gokarn '011 in view of the 2003 Humira® Label. *Id.*

C. Claims 24-30 of the '619 Patent Are Obvious Over the Humira® Label in view of Fransson and Gokarn '011

The pH limitations of claims 24-30 also are obvious over Gokarn '011 in view of the 2003 Humira® Label. Ex. 1202 ¶¶ 146-149. The Gokarn Provisional, the disclosure of which is carried forward into Gokarn '011, taught that IgG antibodies "possess adequate buffering capacity in the pH range of 4.0 to 6.0," and specifically over the narrow range of 5.0 to 5.5, to be the sole source of pH control for the formulation. Ex. 1204, 1:5-8, 13; Ex. 1202 ¶ 148. As discussed in Section X.C. above, Gokarn's ranges closely overlap the claimed ranges, and the '619

patent contains no indication that its claimed pH ranges are critical. Claims 24-30 are therefore obvious. *See In re Harris*, 409 F.3d at 1341.

Moreover, the 2003 Humira® Label teaches that adalimumab is safe and effective in an aqueous formulation at pH 5.2. Ex. 1202 ¶ 71; Ex. 1205, 470. A POSA would therefore have selected the pH of 5.2 for a buffer-free formulation of 50 mg/mL adalimumab with every expectation of success. Ex. 1202 ¶ 148. The pH of 5.2 is the same as that required by claim 30, and falls within the range required in each of claims 24-29. The combination of Gokarn '011 and the 2003 Humira® Label therefore renders obvious claims 24-30 of the '619 patent.

XIII. ANY SECONDARY CONSIDERATIONS ARE INSUFFICIENT TO OVERCOME THE STRONG SHOWING OF OBVIOUSNESS

There are no secondary considerations that would overcome the strong evidence that the challenged claims are obvious over 1) the 2003 Humira® Label in view of Fransson and Gokarn '011, and 2) Gokarn '011 in view of the 2003 Humira® Label. *See Pfizer*, 480 F.3d at 1372.

A. Unexpected Results

There are no unexpected results here. A POSA would have expected that 50–200 mg/mL of adalimumab would have 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. 1202 ¶ 151. The Gokarn Provisional, the disclosure of which is carried forward into Gokarn

'011, demonstrated that 50 mg/mL of EMAB, an IgG1 antibody, possesses sufficient buffering capacity to control formulation pH in the range of 5.0-5.5. *Id.* ¶¶ 88, 110; Ex. 1204, 9, 13. The Gokarn Provisional teaches that antibodies of the same class (e.g., all IgG antibodies) have about the same buffering capacity at a given concentration. Ex. 1202 ¶¶ 82-83, 113, 125; Ex. 1204, 2:15-3:15. 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. 1202 ¶¶ 82-83, 113; Ex. 1204, 3:1–10. Adalimumab is a member of the same IgG1 subclass as EMAB, so a POSA would have expected it to have a very similar amino acid sequence and tertiary structure, and therefore to display similar buffer capacity. Ex. 1202 ¶¶ 88, 109-115; Ex. 1204, 3:6-8. 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 XII.A. 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. 1202 ¶¶ 118-125.

To the extent AbbVie would argue that the reduction of pain was an unexpected result, it was not. As detailed in Section X.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. *Id.* ¶¶ 100-102, 152; Ex. 1207 ¶¶ 32-34; *see, e.g.*, Ex. 1219, 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. 1202 ¶ 153 (citing Ex. 1242, 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. 1202 ¶ 154. By that time, Humira®'s yearly global sales were already far in excess of 10 billion USD. Ex. 1249, 5. 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 claiming the adalimumab antibody ("D2E7") that did not expire until 2016. Ex. 1202 ¶ 153; Ex. 1242, 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 the Gokarn Provisional's prior art disclosure. *See Newell*

Cos., Inc. 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].").

XIV. CONCLUSION

For all the reasons set forth 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: March 2, 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 March 2, 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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Dated: March 2, 2017

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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 13,994 words as counted by the word processing program used for its preparation (Microsoft Word 2007).

Dated: March 2, 2017

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